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The Electrical Conductivity of Living Tissues as it Pertains to Electrocardiography

I. Review of the Problem of Homogeneity vs. Nonhomogeneity, an Outline of the Technical Aspects of Tissue Resistivity Measurements, and a Critical and Experimental Analysis of Certain Pertinent Experiments

By J. Malvern Benjamin, Jr., M.S., Herman Schwan, Ph. D., Calvin F. Kay, M.D., and Joseph H. Hafkenschiel, M.D.

Field analysis methods provide a convenient mathematical process for organization of electrocardiographic observations. The degree of divergence of calculated spatial orientations of heart forces from true orientations is dependent upon the magnitude of inaccuracy of the assumption that body tissues are electrically homogeneous. Preliminary to undertaking quantitative measurements of tissue resistivities in situ, technical difficulties of the problem have been surveyed, and previous studies have been analyzed. It is concluded that an accurate, quantitative measurement of such resistivity has not been made. If major inhomogeneity were found, current methods of application of field theory to electrocardiography might require extensive modification.

ELECTROCARDIOGRAPHIC theory and practice are tending to become increasingly dependent upon the assumption that the heart functions as an electrical dipole, immersed in a fluid of approximately uniform conductivity. This "homogeneous field" concept, originally formulated by Einthoven, has as its basic aim the delineation of the spatial orientation of the electromotive forces generated by the heart. The magnitude of error in such analysis is a direct function of the degree of inhomogeneity of the tissues. This is a problem which has attracted the attention of many investigators. We propose here (1) to survey some of the indirect and direct approaches which have been applied to the problem, (2) to outline the technical difficulties inherent in the direct approach, and (3) to investigate critically the validity and applicability of certain widely accepted experiments in this field.

From the Moore School of Electrical Engineering of the University of Pennsylvania; Aeronautical Medical Equipment Laboratory of the Naval Air Material Center, Philadelphia Naval Base; and the Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

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I. Survey of Experiments for Establishing the Resistivity of Tissues

In the indirect approach to the problem of tissue resistivity, countless descriptions have been made of the effect of body build, heart position, respiration, pericardial calcification or effusion, pneumo-, hydro-, pyo-, or hemothorax, and myxedema upon electrocardiographic patterns. In these and a variety of other conditions, the effect is presumed to be the result of disturbed extracardiac electrical conduction rather

than of disturbed generation of electrical impulses by the myocardium. Some of these data (for example, the reduction of body surface potential differences accompanying pericardial effusion) have suggested that the conducting properties of body fluids and tissues vary appreciably. However, these descriptions have not produced convincing evidence of significant nonhomogeneity of normal body tissues, normally distributed.

Katz and his associates[1, 2] attempted a more definitive differentiation of body tissue conductivity by indirect methods. They found that a large reduction in potential differences at the body surfaces followed the interposition of materials of either high or of low resistivity between the heart and its adjacent structures. They further demonstrated that a large diminution of potential difference at the periphery followed the insulation of the heart from the posterior muscle mass. Conversely, insulation of the heart from the adjacent lung had relatively little effect. Their conclusions that lung tissue is a relatively poor conductor and that electromotive forces generated by the heart follow selective pathways to the periphery are currently not widely accepted. Similar conclusions were drawn from experiments in which air and oil were inserted into the thorax, following which the lung pedicles were separated.[3]

TABLE 1.—*Specific Resistivity* (ρ) *in Ohm Cm. of Various Excised Tissues*

	2500 *Kc**	300 *Kc*†	0.5 *Kc*†
Liver	244–256	200–500	450
Spleen	167–189	240–500	450
Kidney	185–222	150–260	130
Lung	415–556	160–200‡	170‡
Brain	313–357	420–800	810
Muscle	143–200	160–250	
Myocardium		180–250	
Blood	118–149		120–180§
Serum			90§
Fat	2220–4350		

* Osswald.[6]

† Rajewsky, Osken, Schaefer, Schwan, and Stachowiack.[5]

‡ Minced lung tissue, alveolar structure destroyed.

§ Rajewsky and Schwan.[7] A large statistical sampling from mammalian material. The serum values vary by less than 3%.

An indirect experiment of a different type was performed by Eyster, Maresh, and Krasno.[4] They prepared an electrolyte solution with in vitro electrical properties similar to mixed turtle tissue. The distribution of electromotive forces generated by a turtle heart immersed in this solution (a homogeneous electrical field) was found to differ from that with the heart in situ. These and other indirect approaches have suggested a significant degree of nonhomogeneity, but criticism of technic, disagreement regarding the validity of deductions, and the dubious application of experimental results to human electrocardiography have prevented any decisive solution to the problem based upon these indirect measurements.

Numerous direct measurements of electrical properties of biological tissues have also been performed, but many of these, especially those concerned with skin resistance, have no direct bearing upon our problems. A number of workers have performed experiments with excised tissues, varying such parameters as frequency, temperature, and electrode composition. This work has been well summarized by Rajewsky and co-workers.[5] We list below the particular results of excised tissue studies which seem to apply specifically to our problem.

1. Resistance of all tissues is relatively independent of frequency below approximately 10 Kc. and of many tissues below approximately 100 Kc. Above this critical frequency range, resistance progressively decreases as frequency increases. This high frequency effect, known as "dispersion," has been attributed mainly to the nonhomogeneous, membranous structure of tissues.

2. Specific resistivity varies considerably from tissue to tissue.[5, 6] (table 1.)

3. While the resistance of many tissues varies from one specimen to another, the resistance of serum is constant within about 2 per cent from specimen to specimen and remains within the same limit among different species of mammal.[7]

4. Despite the fact that the capacitance of tissues reaches enormous values at lower frequencies, it is not high enough to influence the current flow appreciably at frequencies below

10 Kc. Therefore only the resistivity of tissues may be important for the frequencies generated by the heart.

5. The extent to which the resistance of tissue is subject to change at very low frequencies can be judged by considering the data compiled in table 2. This table lists the specific resistance of several tissues, each measured at two frequencies, while the last column lists the per cent difference between these two resistance values for each tissue. The results are taken from Rajewsky's monograph.[5] Some measurements have been made even at much lower frequencies. One of the authors (Schwan) has found a resistance change of 0.24 per cent for frog muscle between 32 cps. and 100 cps., 6 per cent between 100 and 1000 cps., and 21 per cent between 1 and 10 Kc. This measurement would seem to indicate that the dispersion frequency for muscle is considerably lower than for the tissues listed in table 2.

The application of conclusions drawn from studies of excised tissues to resistivity of body tissues in situ is subject to two main criticisms. First, resistivity might change with time after death of the animal. It has been found[5] to take as long as six hours, and in many cases as long as 40 hours before measurements of resistivity in excised tissues begin to change. When it occurs, the change is greater in the low frequency range than in the higher range in which the dispersion effect is normally present; it is considered to be due to the breakdown of all membranes. Experiments have shown that the change does not begin until metabolism has almost completely stopped.[5] Thus, in the first few hours after death, resistivity should remain approximately the same as before death, provided that the distribution of cells and fluids is not significantly altered. This constitutes the second major criticism. It is obvious that this requirement is easily fulfilled with blood, but impossible to fulfill with, for example, lung. Thus, the material collected in table 1 is difficult to evaluate. Tissues were cut into small sections to fill the conductivity cells, and no especial care was taken to avoid loss of blood. The results are therefore of limited significance as measurements of absolute values of resistivity of the living tissues in situ. They are of value in demonstrating the effects of frequency upon resistivity measurements and the constancy of resistivity for several hours after the death of the animals.

Eyster, Maresh and Krasno[4] studied the resistivity of living tissue in situ. They attached electrodes to one forelimb and one hindlimb of a living dog. At a fixed frequency and potential difference, the effect on impedance of severing successive body tissues was studied. They concluded that nearly 60 per cent of the total conductance of the trunk was in the dorsal muscles and vertebral column. They also found that the total impedance was decreased by 11 per cent when a rapid blood transfusion was administered. They concluded that differences in resistivity were of sufficient magnitude to be important in electrocardiographic studies. This method does not lend itself well to exact quantitation of resistivity of individual tissues and has been subject to the criticism that the frequencies employed in measurement were much higher than those with which we are concerned in electrocardiography. The latter criticism was avoided in the studies of Burger and Van Milaan.[8] They measured the specific resistance of various parts of the body to direct current. The gradient of potential difference drop between electrodes was measured from intermediary electrodes. After computations of the cross sectional area of the tissue investigated, an approximation of the specific resistance of individual tissues was made. In their subsequent investigations with body models,[9] they considered the specific resistivity of lungs to be four times that of other body tissues concerned

TABLE 2.—*Specific Resistance of Tissues at Low and High Frequencies*

	Kc	*ρ*	*Kc*	*ρ*	%
Liver	0.5	452	228	345	24.0
Spleen	0.8	449	28	392	13.0
Kidney	0.5	192	210	147	23.0
Lung	0.5	174	228	161	7.5
Brain	0.41	810	28	790	2.5

From Rajewsky's monograph.[5] Per cent difference between low and high frequency resistivity is expressed for each tissue.

in the conduction of electrical forces generated by the heart to the periphery. A major influence of nonhomogeneity of this magnitude upon the distribution of forces was demonstrated.

Kaufman and Johnston[10] applied special electrodes directly to the tissues of living dogs. From their results, they concluded that "errors in theoretical studies of the form of the electrocardiogram, made by considering the tissues which surround the heart uniform with respect to their specific resistivity, are of no practical importance." Because of the importance and wide acceptance of this study, it has been subjected to critical analysis described below.

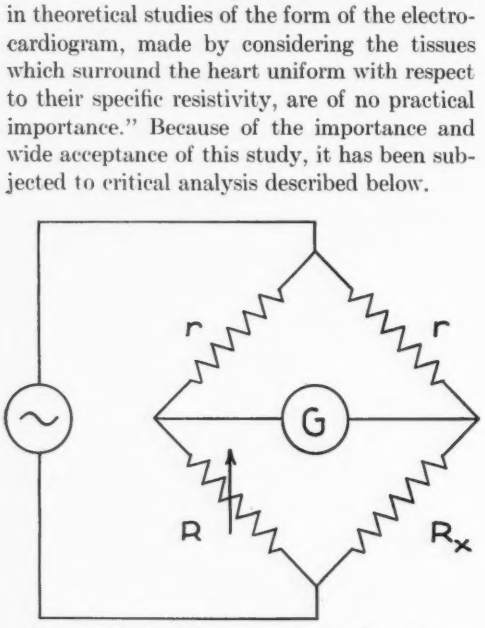

FIG. 1. Simple Wheatstone bridge for measurement of resistance.

The difficulties inherent in the performance of such an experiment as was done by Kaufman and Johnston are great. Thus it would seem advisable to sketch out briefly the principles and technics involved in the performance of this type of measurement.

II. Technical Difficulties Inherent in Measurement of Tissue Resistance

An ascending scale of complexity attends each step from the measurement of the resistance of a length of solid wire to that of a volume of electrolyte in simple solution, to that of excised tissue, and finally to living tissue in situ.

Wire. Let us first consider the measurement of the resistance (*Rx*) of a short length of solid wire. This may be accomplished easily by the use of a Wheatstone bridge, as shown in figure 1. The variable resistor (*R*) is adjusted to produce a minimum deflection of the meter (*G*). The resistance of the wire (*Rx*) is then equal to that of the variable resistor, provided that the values of the fixed resistors (*r*) are equal. The frequency and voltage of the generator may be varied at will without changing the balance of the bridge.

Electrolyte. Suppose next it is desired to measure the resistance between two wires immersed into an electrolytic solution. If this system is attached to the bridge, it is found that the bridge cannot be balanced permanently when direct current is applied because the measured resistance drifts to higher and higher values with the passage of time.

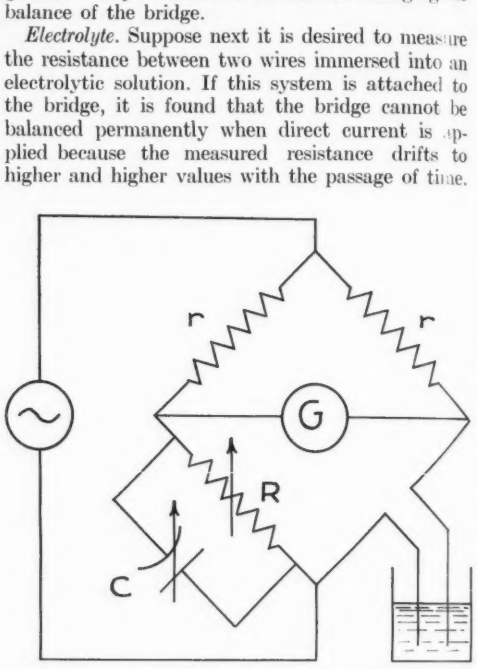

FIG. 2. Modified bridge for measurement of resistance and capacitance.

However, with alternating current instead of direct current, a balance independent of time may be attained by the addition of a variable condenser, (*C*) (fig. 2). The fact that it has been necessary to add to the bridge in parallel with the variable resistance a capacitance, in order to achieve balance, suggests that the electrolytic system must be represented by some combination of resistances and condensers rather than merely by a resistance as was the case with the solid wire. A more careful investigation will show that the electrolytic solution between the two wires which serve as electrodes has itself a certain capacitance and that this capacitance is equal to the capacitance of the variable condenser, (*C*), at very high frequencies. As the frequency is decreased, however, the capacitance *C* increases though the capacitance of the solution itself remains constant. This effect is due to phenomena which take place at the interfaces between the electrolyte and the electrodes and is called "polarization." Under the influence of the current passing through these inter-

faces, a voltage is developed which is proportional to the amount of current flowing and can be characterized by a resistance. Further investigation shows that this resistance, R_{pol}, is in series with a capacitance C_{pol}. The resistance R_{sol} and the capacity C_{sol} of the electrolyte are therefore at each electrode in series with the impedence of the interface represented by polarization resistance R_{pol} and polarization capacity C_{pol} (fig. 3). The total combination is equal to the R-C combination in the adjustable arm of the bridge. The values R and C are therefore not identical with resistance and capacitance of the electrolyte, for the polarization resistance and polarization capacitance must also be taken into account. The extent to which polarization influences the values of R and C depends on temperature, design and material of the electrodes and their distance of separation, concentration of the electrolyte, and quite markedly on the frequency in use. But polarization is nearly independent of the applied voltage so long as this voltage is not too high. Figure 4 shows how polarization influences the measured resistance R as a function of applied voltage and frequency. So long as the voltage across the electroytic cell does not exceed approximately 1 to 10 volts, depending on circumstances such as cell design and electrolyte, the resistance is not influenced by a change in the voltage. At higher voltages the polarization resistance is more noticeable with smaller electrode area than with larger area. Resistance as a function of frequency is constant at high values of f and starts to increase at first slowly and then more and more rapidly when the frequency changes. The effect is again more pronounced with smaller electrode area.

With small electrode area and low frequencies, polarization can be especially disturbing. Under these conditions, it is therefore necessary either to diminish polarization so much that it cannot influence the results or to correct for it by determining its exact influence. The most exact method to date for eliminating polarization resistance is to make two determinations of total resistance with two different spacings between electrodes.[11] By subtracting the measured resistances corresponding to these two different electrode spacings, one obtains a resistance which corresponds to the difference between the two distances at which the measurements were taken, independent of polarization. The method has the disadvantage that two measurements have to be made in order to get one result. It is applicable when the resistance change which takes place upon varying the electrode distance is comparable to the measured resistance itself, that is, when the resistance which corresponds to the difference between two electrode spacings is not small compared to the resistance values measured in the bridge. If this is not the case, the precision of measurement is low and the overall gain in accuracy achieved by elimination of the polarization resistance from the measured resistance is offset by the increased inaccuracy thus introduced into the final resistance value. Another way to avoid polarization is by use of a four electrode system, in which two electrodes introduce current into the medium while two other electrodes measure the voltage drop across a portion of the medium caused by the current flow between the first electrode pair.[8] This measurement can be made with a voltmeter which has a very high input resistance, for example, a vacuum tube voltmeter. Polarization will not be present then at the two voltage measuring electrodes since practically no current is passing through them because of the high input resistance of the voltmeter. However, with this method it is quite difficult to measure tissue capacitance.

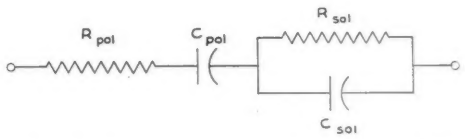

FIG. 3. Equivalent circuit of solution and electrodes with polarization present. R_{sol} = solution resistance; C_{sol} = solution capacitance; R_{pol} = polarization resistance; C_{pol} = polarization capacitance.

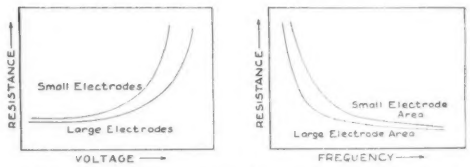

FIG. 4. Influence of voltage and frequency on measured resistance in the presence of polarization.

Another method employed in the investigation of biologic material is based on the assumption that the polarization resistance of an electrolytic cell with biologic material is identical with the polarization which the same electrodes show when they are simply immersed in solution of the kind that surrounds the biologic material.[12] For example, an exchange of tissue for physiologic saline solution should not change the electrode polarization. If this assumption is true, the polarization of a special set of electrodes can be measured while immersed in Ringer solution. Resistance and capacitance of this Ringer solution are well known, and since the total resistance, as illustrated in figure 3, has to be equal to the R-C combination in the variable bridge arm, R_{pol} and C_{pol} can be determined by calculation. The knowledge of these values then enables us to correct any measured resistances and capacitances of tissue for polarization. As far as we know, no detailed material has been published which bears on the above mentioned assumption that electrodes

show the same degree of polarization when placed in tissue as when placed in Ringer solution. In fact, one of us (H.S.) made a series of measurements with highly concentrated blood and found that the polarization capacitance is much smaller in blood than in serum and further, that it is a function of the volume concentration of the blood. It is, therefore, our belief that material which has been investigated on the aforementioned basis should be reviewed to determine the extent to which a smaller polarization capacitance than originally assumed might affect the results.

In most cases it is much simpler to reduce polarization effects than to correct for them. Platinum electrodes, especially when covered with a layer of platinum black, cause much less polarization than other metal electrodes. Furthermore, if it is possible to make the electrodes large and to maintain a sufficiently great distance of separation between them, it is nearly always possible to suppress the influence of polarization on the resistance at least. In cases where electrode area and distance cannot be sufficiently large, the use of higher frequencies is of value. However, it is necessary in each situation to investigate the extent to which polarization is apparent before final measurements are taken. The simplest way of checking polarization is to change the frequency and see if the resistance of the electrolytic system changes. Electrolytes are frequency independent up to extremely high frequencies (order of 10^8 cps), so any change in measured R or C found with electrodes immersed in an electrolyte while varying the frequency must be caused by polarization at the electrode-electrolyte interface.

The effect of temperature on the electrolyte itself is not great (approximately 2 per cent decrease in resistance per degree centigrade increase). To control this we simply make all the measurements at a constant temperature. The size, shape, and spacing of the wires, and the shape and size of the container will also exert direct influence on the resistance and capacity. To eliminate these variables, after the geometry of the container and electrodes has been fixed, a solution of known specific resistance can be introduced into the container, and resistance and capacity determined at a specific voltage, frequency, and temperature. If we then let ρ_k represent the resistivity* of the standard solution and R_k its resistance, while similar quantities with subscript x stand for the corresponding resistive values of the solution to be tested, the relationship among these quantities may be expressed as follows:

$$\frac{R_x}{R_k} = \frac{\rho_x}{\rho_k} \quad \text{or} \quad \rho_x = R_x \frac{\rho_k}{R_k}.$$

The value $\mu = \dfrac{R_k}{\rho_k}$ should be dependent only upon the geometry of the cell, and hence it is called the cell constant. Thus by this means one may calibrate any system consisting of electrodes placed in a container of any shape or size, with the aid of a standard solution.

Apparently, therefore, in measuring the resistance of electrolytes, unless we go to sufficiently low voltages, high frequencies, and large electrode areas, R and C as measured by the bridge will be functions of the electrode characteristics as well as of the solution. Thus, to measure successfully the R and C of the solution only, we must select and adjust the electrode material, size, surface condition, voltage, and frequency; otherwise, our measurements will be distorted by an R and C derived from the measuring system.

Excised tissue. Now let us pass on to the consideration of the measurement of body tissue. Based on experience gained from the experiments described above, if we should wish to carry out a crucial experiment we would probably excise a specimen of the tissue to be investigated, large enough to fill the conductivity cell, place it in the cell, plunge the electrodes into it, adjust the frequency and voltage, make the measurement, and finally calibrate the cell with a known solution. This is a satisfactory procedure and, if correctly executed, will yield the correct results. How, though, should the electrode area, voltage, and frequency be decided upon? Let us first consider factors other than polarization which determine the size of these variables. The volume of tissue available will determine the maximum area for the electrodes. If we are measuring resistance for application to problems in electrocardiography, it would seem desirable to select a frequency in the range of those present in the pattern of voltage fluctuations produced by the heart. This can usually be done. The voltage, in turn, should be as small as it is practical to work with, consistent with the accuracy required in order not to damage or to heat up the tissues. After all of these variables have been decided upon, the apparatus should be checked for polarization by holding constant all but one variable and varying this one, preferably frequency, over a reasonable range (for example, a factor of three on each side of the working value).

* The resistivity (ρ) of a homogeneous conducting material is related to its resistance (R) by the following formula, where l = length of material sample and A = cross-section area.

$$R = \int_0^l \rho \frac{dl}{A}.$$

If the material has a constant cross-section area along its whole length, the above formula reduces to $R = \rho \dfrac{l}{A}$. Thus ρ is a function of the nature of the material, not of its shape. The unit of resistivity is the ohm centimeter. This is the resistance measured between 2 opposite faces of a centimeter cube of the material.

If the measured R remains constant, one has the assurance that there is only an insignificant polarization effect present. In this sort of experiment, it has been found possible to make the electrode area sufficiently large to meet the frequency and voltage requirements and thus to perform the experiment, though not down to frequencies near those present in the electrocardiogram. Such measurements have been made by Cole, Fricke, Curtis, Rajewsky and many others.

Tissue in situ. The measurements described above leave much to be desired in answering the question of whether or not the human body is a homogeneous conductor. Because of the radical change in blood distribution and disturbed physiology of the tissue, there is no way of knowing how much the tissue may be changed when it is removed from its natural environment. Thus it would be much better to measure the tissue in situ. A measurement can, of course, be made by introducing the electrodes into the tissue, but under these conditions there is no cell with measurable boundaries and a new method must thus be found to calibrate the electrodes.

To understand this new situation, let us perform the following experiment. Place a pair of electrodes, of fixed size and maintained a fixed distance apart, into successively larger containers each filled with solution of the same resistivity, and measure R and C between the electrodes. One finds on doing this that as the cell gets large compared to the distance between the electrodes and to their area, the R and C values become independent of size and shape of the container. Thus if the electrodes that are placed in the tissue are sufficiently small and close together the boundaries of the tissue may be neglected, and to calibrate the electrodes, we merely have to place them with the same relative spacing in a "very large" cell filled with solution of known resistivity. A more detailed discussion of this problem is found in reference 10.

In performing this experiment, however, the areas of the electrodes will have to be very much less than they were when the tissue was placed in a conductivity cell since they must be small enough not to do serious damage to the organ in which they have been introduced. On the other hand, they must not be so small as to approach the size of the individual cells within the tissue under observation, for then one might get radically different measurements depending upon whether the electrode happens to be right against a cell, or in an interstice between cells. Because of this small electrode size, the minimum frequency at which the measurement can be performed without introducing polarization will be much higher than in the previous experiment. If we are measuring resistance for application to problems in electrocardiography, it would at first seem necessary to perform the measurement with current of a frequency near to the frequency components present in an electrocardiogram. Thus the excised tissue work and the Kaufman and Johnston experiment have been dismissed by some (e.g. Katz[13]) because they were performed at frequencies much higher than those present in the electrocardiogram. However, it appears possible that measurements made at any frequency up to about 10,000 cycles per second might be applicable to problems in electrocardiography. As discussed above, the effect of frequency begins to appear only at about 10 kilocycles and affects R only to a small degree. Table 2 shows this effect in more detail for various tissues. In addition frog muscle resistivity has been measured by one of the authors (H.S.) in the region from 100 Kc to 30 cps and has been found to be constant under 10 Kc as discussed above. Measurements have also been made by Schwan[14] on blood from 50 cps to 2500 cps and by Dänzer[15] from 1 Kc up to several megacycles. These measurements show no frequency effect below 100 Kc and at 100 Kc the effect is only about 1 per cent.

Convincing as these reasons may sound, the fact remains that no reliable measurements have actually been made upon living tissue in situ at low frequencies. Thus, we cannot say with certainty that an extrapolation from higher frequencies is really valid.

In performing any of these experiments, the electrodes would, of course, be made of some chemically inert electrical conductor. A convenient material for the purpose is platinum. Besides being chemically inert, platinum has the further advantage that it is possible to increase its effective surface area up to one hundredfold by plating onto it a spongy layer of platinum known as "platinum black." This platinum black layer will then markedly reduce the effect of polarization by increasing the surface area. However, care must still be taken not to let the electrode size decrease to that of a single cell of the tissue to be measured.

III. Actual Measurements of Tissue in Situ

The work which most closely approaches the application of the basic principles considered above is that of Kaufman and Johnston. In their experiment they made a pair of platinum-platinum black electrodes from wire 0.25 mm. in diameter insulated with glass down to the tips. They carefully determined the correct electrode spacing such that the tissue into which the electrodes were introduced could be considered infinite in extent compared to the distance between electrodes. They then measured the resistances in situ of tissues of living anesthetized dogs.

As a result of these studies, they drew the

following conclusions. "Measurements on the living tissues of the anesthetized dog show that muscle, normally inflated lung, and liver have resistances of the same order of magnitude. These measurements establish experimentally the validity of the assumption that the errors in theoretical studies of the form of the electrocardiogram made by considering the tissues which surround the heart uniform with respect to their specific resistivity are of no practical importance."

After an analysis of this work, we find it difficult to accept their conclusions for the following reasons:

(1) The divergence and variability of their results do not seem to prove that the resistivity of the tissues is uniform.

TABLE 3.—*Resistivities of Tissues in Ohm Cm. as Reported by Kaufman and Johnston*[10]

	Range	Average	No. of Determinations
Muscle	320–1532	649 ± 163	24
Liver	222–1083	596 ± 144	13
Blood	175–235	207 ± 19	4
Lung	615–897	756 ± 52	16
Heart	143–307	215 ± 35	12
Pericardium	405–434	419 ± 14	2
Fat	1757–2450	2006 ± 207	4
Serum	98–178	138 ± 40	2

(2) It can be demonstrated that polarization was present to a sufficient degree as to make difficult the interpretation of their results as measurements simply of tissue resistance.

Table 3 is a summary of their results. The two figures for each tissue in the column marked "range" represent the extreme values obtained from the series of measurements. These values are excerpted from their table 3.[10] The next column gives the arithmetic mean and probable error of the single observation of each series of measurements. The last column tabulates the number of determinations that are averaged in each case.

Examination of table 3 shows probable errors of sufficient magnitude to mask approximately a 2 to 1 difference in resistivity between lung, liver and muscle tissues, while the extreme variations among measurements of these three tissues (222–1532) is a factor of 7. Furthermore, if the other types of tissue listed are considered, the difference in conductivity between tissues becomes much greater. At the worst, there is a 20 to 1 resistivity difference shown between serum and fat. The authors regard lung, liver, and muscle as the principle tissues concerned with the transmission of currents derived from the heart. The degree to which this assumption is justified is difficult to estimate. For example, by their results, the resistivity of fat is several times higher than that of other tissues. It seems possible that the irregularly placed fat pads immediately adjacent to the heart might exert an important influence upon the distribution of electromotive forces even if the other tissues were uniform.

However, the other tissues are not uniform, for while lung, liver and muscle conductivity difference is still less than one order of magnitude, an actual difference in tissue resistivities of 4 to 1, 2 to 1, or even less might make a significant difference in the distribution of heart potentials to the surface of the body. In order to evaluate the effect of combining several volume conductors of different resistivities, it would be necessary to know in detail the geometry of the distribution. Even a relatively simple configuration would be quite difficult to analyze mathematically.[4] As previously stated, Burger and Van Milaan[9] noted a very significant change in the distribution of potential differences on a model when a homogeneous medium was altered by the insertion in the space normally occupied by lung, of a mass with resistivity four times that of the original electrolyte.

Let us next consider the problem of polarization in the experiment under discussion. Certain of the results led to the suspicion that polarization had exerted an appreciable influence. If this were the case, the reported figures for tissue resistivity derived not from the tissue but from the measuring system. These suspicions were aroused especially by the following:

1. The capacities recorded when the electrodes were placed in the calibrating solutions were very much greater than one would expect in the absence of polarization, as can be concluded from figure 2 in Kaufman and Johnston's

paper. A reactance of the order of 1.0 ohm would be anticipated in the absence of polarization rather than several hundred ohms as reported.*

2. A variation in cell constant was observed with changes of temperature and test solution concentration. It will be recalled that the cell constant should be independent of these factors.

For these reasons, it was decided to duplicate the electrodes used in this experiment, check them for polarization and at the same time see whether longer electrodes might eliminate polarization if it were found to be present with the short ones. Accordingly, electrodes were made by sealing lengths of 0.25 mm. diameter platinum wires (the diameter used by Kaufman and Johnston) in glass tubes. Two of these electrodes were mounted a fixed distance apart, coated with platinum black, and placed in a liter beaker of physiologic saline solution. They were then connected to a bridge whose operating frequency could be varied from 50 to 500,000 cycles per second. The relative accuracy of the bridge was at least one part in 100,000 for the resistance. (For this purpose, of course, such accuracy was not required, so the results have not been reported to this precision.) Details of the bridge will be described in another paper.[16]

The experiment was started with long electrodes. R and C were measured with the electrodes placed in the beaker of 0.9 per cent saline solution while the frequency was varied in several steps from 100 to 100,000 cps. The electrodes were then shortened, replatinized, and remeasured. The shortening was done in 5 successive steps, starting with a length of 7.6 mm. and ending with only the cross-section of the wire exposed, as was used by Kaufman and Johnston.

Additional runs were made at one length, varying the voltage and varying the electrode spacing. It was determined that for the particular values we chose, neither of these latter quantities was critical. That is, the measured value of R and C remained constant as both the voltage and the spacing were varied through the operating point to a reasonable distance on each side. The voltage finally chosen was 0.1 volts, while the spacing was 1.25 inches for the first three runs and 0.25 inches for the last two runs.

The results are presented graphically in figures 6 and 7. The series resistance (R_{ser}) and series reactance (X_{ser}) were calculated using the formula in figure 5 where R_{par} and C_{par} are the R and C observed on the bridge with a small correction made in C to allow for a small fixed bridge capacitance. Figure 6 is a plot of R_{ser} against frequency for five electrode lengths. The uppermost curve (marked 0.025 mm.) is the one approximately corresponding to the Kaufman and Johnston electrodes. Figure 7 is a similar presentation showing variation of

* Capacitive reactance (X_C) can be thought of as being somewhat similar to resistance in that an alternating current (I), passing through a condenser producing a voltage (V) across the condenser of magnitude: $V = X_C I$. However, unlike a resistor, no energy is dissipated by the condenser. Also, the alternating voltage across a condenser does not rise and fall at the same instant of time as does the current going through it. This latter effect does not directly concern us here. Capacity and reactance are dependent upon each other. This dependence is expressed by the formula $X_C = \frac{1}{2\pi f C}$.

The reactance values as given by Kaufman and Johnston are thought to be in series with the resistances they investigated. In order to find out what series reactance represents the capacitive properties of a 0.9 per cent saline solution the following steps have to be taken: The capacity of the saline solution is given by the equation $C_{par} = \frac{\epsilon}{4\pi\mu}$, where ϵ is the dielectric constant and μ the cell constant. In this case, $\epsilon = 80$ and $\mu = 17$ cm.$^{-1}$. Substituting

$$C_{par} = \frac{80}{4 \times 17\pi} = 0.4\ cm. = \frac{0.4}{9 \cdot 10^{11}}\ farad,$$

This capacity is shunted across the resistance of the saline solution

$$R = \rho \cdot \mu = 80 \cdot 17 = 1360\ ohm.$$

In order to calculate the corresponding series capacity C_{ser} as indicated in figure 5, the formula

$$C_{ser} = C_{par}\left[1 + \frac{1}{(2\pi f \cdot R \cdot C_{par})^2}\right]$$

has to be applied. It yields: $C = 310\mu f$ when the special case $f = 1000\ cps$ is considered. From there the series reactance as given by $X_C = \frac{1}{2\pi f C_{ser}}$ can be determined and results in a value of about 0.5 ohm.

series capacitive reactance (X_{ser}) with frequency for the same series of electrodes.

In order to interpret R_{ser} and X_{ser}, let us return once more to figure 3, the equivalent circuit of the solution and the electrodes. The actual capacity of the solution can be calculated approximately. It is about 4 micromicrofarads. This is so small compared to the measured capacity, that it may be safely disregarded. Thus, in figure 3, C_{sol} equals zero.

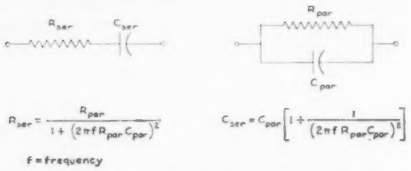

FIG. 5. Relationship between simple series and parallel R - C circuits.

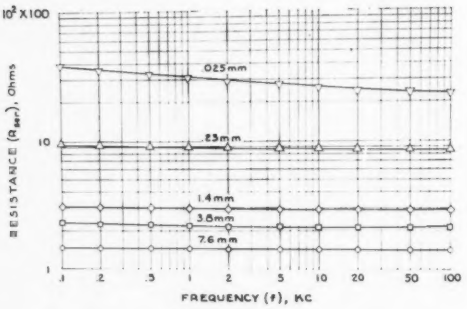

FIG. 6. Resistance of Kaufman and Johnston type electrodes of varying lengths vs. frequency when immersed in 0.1 N NaCl solution.

Therefore, R_{ser} equals R_{sol} plus R_{pol}. Stated in words, this says that the series resistance is made up of two components, the resistance we are trying to measure, and the polarization resistance, while the capacitive reactance is due completely to polarization of the electrodes.

It is interesting to compare the reactance and resistance values as plotted in figures 6 and 7 with the values determined by Kaufman and Johnston. This comparison is done in table 4 for the frequencies which Kaufman and Johnston used in presenting the impedance loci of their pair of electrodes and for our electrode system having the lengths of 0.23 mm. and 0.025 mm. The columns I, II and III give the values as determined for the Kaufman-Johnston cell, our cell with the length (l) = 0.23 mm., and our cell with length (l) = 0.025 mm., respectively. A comparison of the

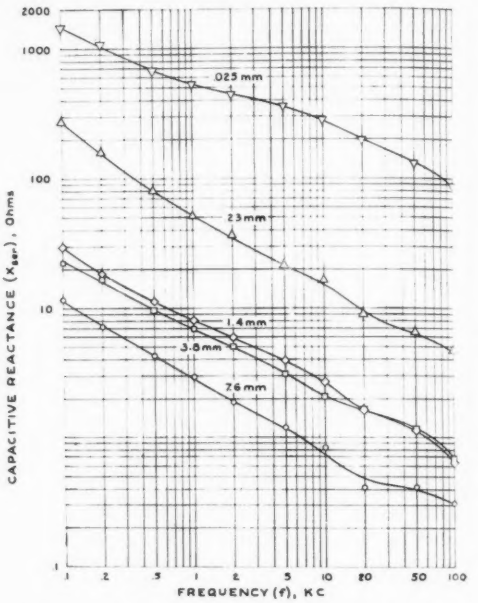

FIG. 7. Capacitive reactance of Kaufman and Johnston type electrodes of varying lengths vs. frequency when immersed in 0.1 N NaCl solution.

TABLE 4.—*Resistance and Reactance Values at Frequencies 500 to 10,000 cps.*

Column I: electrode system of Kaufman and Johnston. Columns II and III: our system with electrodes of lengths 0.23 mm. and 0.025 mm.

Frequency	I (K-J)		II (l = 0.23 mm.)		III (l = 0.025 mm.)	
	X	*R*	*X*	*R*	*X*	*R*
cps.						
500	480	2010	78.4	900	677	3290
1,000	335	1890	50.2	888	529	3110
2,000	230	1830	35.3	877	442	2950
5,000	140	1760	20.9	867	358	2735
10,000	115	1730	15.0	860	280	2585

results shows that the Kaufman and Johnston system has values which are between those measured with our two sets of electrodes. This indicates that the effective length of the Kaufman-Johnston system is somewhere between 0.23 and 0.025 mm. Our presentation in figure

7 shows that the reactance plotted in a log-log representation decreases linearly as frequency increases (i.e. the reactance decreases as a power function of the frequency). The slope of the log-log representation being approximately $-\frac{1}{2}$ is in agreement with investigations of other authors pertaining to the influence of electrode polarization on the series reactance.[17] This together with the fact that the absolute values of the reactance agree with those to be expected in the presence of polarization, shows that polarization is responsible for the reactance values in our electrode system. Since the Kaufman and Johnston system in saline shows the same behavior as our system, it is apparent that polarization was responsible for the reactance values in their system also. The relation of resistance to frequency was likewise essentially the same in the two experiments, and in each case behaved as would be predicted in the presence of polarization. Thus, the frequency dependence of both the resistance and the reactance is caused by polarization.

The difference between the R values determined by Kaufman and Johnston at 1 and 10 Kc is about 9 per cent. Our figure 7 shows that the difference between the 10 Kc value and the 100 Kc value contribute an additional 5 per cent to 10 per cent in the same direction. The resistance at extremely high frequencies is undisturbed by polarization. We may thus assume that the resistance values for the electrodes in saline, determined by Kaufman and Johnston at 1 Kc are about 15 per cent too high. This is in agreement with an estimate based upon Warburg's law. It predicts that the polarization resistance changes inversely with the square root of the frequency. The law has been shown to be valid as a first approximation by many authors.[18] By its use we may extrapolate from the difference of 9 per cent as determined by Kaufman and Johnston between 1 and 10 Kc to infinite frequency to determine the true electrolytic resistance which was present in their case. Thus we find that the 1 Kc value differs about 13 per cent from the electrolytic resistor. This figure agrees well with our other estimate.*

Kaufman and Johnston recognized that polarization was present. The measurements which were corrected for polarization, and the amounts of such corrections are not specified. The foregoing discussion used their impedance loci as represented in their figure 2 in the "post biological" case. This case represents the calibration of their electrodes after a tissue measurement had been performed and differs in its resistance and reactance values (roughly 10 per cent and 30 per cent respectively) from the "pre-biological" calibration performed before the tissue measurement. In the postbiological calibration, both reactance and resistance are higher. It is well known that polarization resistance and reactance depend to a high degree on the amount of platinum black which covers the electrodes.[18, 19] This result is produced by an increase in effective electrode area. It seems possible that the introduction of the electrodes into the tissue changed the platinum black deposit, which is quite soft, either by rubbing off some of the platinum black or by adsorption of proteins. Such a change could result in a decrease of the effective area of the electrode. Figure 2 in Kaufman and Johnston's paper represents one of their calibration tests which they took before and after each measurement. The degree of change between pre- and postbiologic calibrations in their other measurements may be determined by simple subtraction of the pairs of figures in their table 3. These differences, expressed in percentage of the postbiologic measurement, are shown in table 5.

We conclude from these values that the figure 2 in Kaufman and Johnston's paper represents

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* Warburg's Law connects polarization resistance R with the frequency f as follows:

$$R_{pol} = \frac{k}{\sqrt{f}}$$

From this we get for two different frequencies f_1 and f_2

$$\frac{R_{pol}(f_1)}{R_{pol}(f_2)} = \sqrt{\frac{f_2}{f_1}}$$

The ratio of f_2 and f_1 is 10:1 in the discussed case. Hence $R_f = 3.2R_f$ or $R_{f_1} - R_{f_2} = 2.2R_{f_2}$. Kaufman and Johnston found $R_{f_1} - R_{f_2} = 1890 - 1730 = 160$ *ohm*. Substituting this figure into the above equations, we find that $R_{f_1} = 250\ \Omega$ which is 13 per cent of R at 1000 cps.

a case with a relatively minor difference. In the majority of the other measurements, the difference between the resistance values with the cell immersed in the standard calibration solution before and after the tissue measurement was greater than that shown in their figure 2, and in many cases the difference was very much greater. From this it is reasonable to believe that in the majority of their measurements, the polarization was greater than in the case demonstrated by the authors in figure 2. The discussion of this figure led to our estimate of approximately 15% polarization disturbance when the above pair of electrodes was immersed in a 0.9% saline solution. It must be emphasized that this percentage figure

TABLE 5.—*Percentage Differences Between Prebiologic and Postbiologic Calibrations (See text)*

Muscle	Liver	Lung	Heart	Pericardium	Fat	Blood	Serum
−2.8	13.9	3.0	7.0	7.2	11.6	20.5	82
+2.2	37.3	7.0	7.7		32.0	28.6	
25.1	23.5	7.0	6.5				
37.5	2.6	18.2	5.6				
23.2	79.0	2.7	22.5				
2.4	168.0	25.7					
11.4		12.3					
5.7		11.6					
17.6		11.5					
102.0		15.4					
91.0							

represents only the additional polarization factor in the postbiologic and in the prebiologic measurements in saline, and is not an estimate of the total effect of polarization when the electrodes were used in tissue measurements.

Kaufman and Johnston took certain steps in order to correct for polarization. Their results were computed in the following way: "0.9% saline solution at body temperature was measured in a standard conductivity cell (R_k). The cell constant of the conductivity cell (K) was known to be 39.37. The same solution was measured with the point electrodes before and after each observation. The pre-biologic constant of the point electrodes was ascertained from the first reading, $R\mu$ (at 1000 cps) by the formula $\mu = K\frac{R_\mu}{R_k}$. The post-biologic value was ascertained from the second reading in the same way. The specific resistance of the tissue was computed by dividing the measured resistance of the tissue at 1000 cps by the cell constant."*

We feel that this method is subject to the following criticisms. Consider again our figure 5. By multiplying R_{ser} with C_{ser}, the formula: $(2\pi f)^2 R_{ser} R_{par} C_{ser} C_{par} = 1$ results. Introducing X_{ser} and X_{par} instead of the equivalents, $\frac{1}{2\pi f \cdot C_{ser}}$ and $\frac{1}{2\pi f \cdot C_{par}}$, respectively, the relationship:

$$R_{ser}/X_{ser} = X_{par}/R_{par}$$

results. The presence of polarization increases both reactance and resistance. Therefore, the reactance values as published by Kaufman and Johnston cannot be too small. In the measurements at 1000 cps. from the tissue studies illustrated in their figures 3, 4 and 5, we find that the ratio X_{ser}/R_{ser} is in each case smaller than 0.1. In saline solution (their figure 2) it was less than 0.15. Thus the ratio: $R_{par}/X_{par} = 2\pi f\ R_{par}.\ C_{par}$ was, in all these examples, less than 0.15. Its square, which gives the difference between R_{ser} and R_{par} in relative units, is therefore less than 2.25 per cent. This demonstrates that it does not matter very much whether we express the resistance values in series resistances (R_{ser}) or parallel resistances (R_{par}). The difference is always smaller than 2.25 per cent as long as we consider only the frequency 1000 cps. The parallel combination R_{sol} with C_{sol} (fig. 4) may thus be transformed to a series combination without actually changing the resistive component and vice versa. Thus we recognize that, at least for the 1000 cycle values, the resistances of the tissue and of the saline solution, are falsified only by the polarization resistance R_{pol}.

Let us now consider what this means for the calibration procedure as applied by Kaufman and Johnston. We can assume that their standard conductivity cell was so constructed that polarization did not noticeably influence resistance measurements. Thus, the specific resistance of the saline solution, used for calibration of the point electrodes, has been deter-

* The μ in this equation is affected by polarization.

mined correctly. Immersing the point electrodes in this saline solution we find a resistance

$$R(sal.) = \mu\, \rho(sal.) + R_{pol}\ (sal.).*$$

Introducing the point electrode system in tissue

$$R(tis.) = \mu\, \rho(tis.) + R_{pol}\ (tis.).$$

These equations provide a basis for the determination of the inherent error in the method for computation of specific resistance as employed by Kaufman and Johnston. We get from the first equation for μ:

$$\mu = \frac{R(sal.) - R_{pol}(sal.)}{\rho(sal.)} = \mu_0 \left[1 - \frac{R_{pol}(sal.)}{R(sal.)}\right],$$

and from the second one

$$\rho(tis.) = \frac{R(tis.) - R_{pol}(tis.)}{\mu}$$

$$= \frac{R(tis.)}{\mu_0} \cdot \frac{1 - R_{pol}(tis.)/R(tis.)}{1 - R_{pol}(sal.)/R(sal.)}$$

The determination of the specific resistance, applying the formula $\rho\ (tis.) = \dfrac{R(tis.)}{\mu_0}$ as they did, leads to a result which has to be corrected for

$$\frac{1 - \dfrac{R_{pol}(tis.)}{R(tis.)}}{1 - \dfrac{R_{pol}(sal)}{R(sal)}}$$

The resistance of the tissue is high compared with the resistance of the saline solution. The relative error of the discussed method is then given by the ratio $R_{pol}\ (sal.)/R(sal.)$. As previously discussed, this ratio is about 0.15 and may go up to much higher values. This is the inherent error when no attempt is made to correct for polarization at all. Therefore, the correction method used by Kaufman and Johnston did not eliminate the errors due to polarization.

In view of all the foregoing, we are led to feel that although the Kaufman and Johnston experiment was of considerable value as a first attempt to delineate this complex problem, a considerable amount of further work will be required to reach a definite conclusion concerning the variation of resistance from tissue to tissue.

* μ is here defined as the cell constant uninfluenced by polarization.

Conclusions

The conclusions drawn from this survey are as follows: The question of electrical homogeneity of the body is not a yes or no type of question. It is not meaningful to ask simply, "Is the body a homogeneous conducting medium, or is it not?" It is well understood by all who have investigated the problem in recent years that the body is only "relatively" homogeneous. Thus the problem is one of determining whether the inhomogeneity is sufficient to require modification of the theoretic interpretation of electrocardiographic observations, and if so, in what way, and by how much.

Regarded from this viewpoint, the early, relatively *qualitative* attempts to answer the question are of little value except as indications that the body is not absolutely homogeneous. As between the recent direct and indirect approaches to the problem, it would seem that the direct approach of actually measuring the resistances of the various tissues within the body would be the most straightforward. Measurements of excised tissue indicate variations in resistance of different tissues over quite a wide range, but the figures may not be directly transposed to apply to tissues in situ or to electrocardiographic problems in general. The final step in the direct approach appears to be the measurement of resistance of living tissues in situ. The first attempt in this direction, while valuable as a pioneer effort, has not, in our opinion, yielded an unequivocal result. Thus, we feel the whole matter of relative resistivity of tissues is still an open question.

It has been found convenient to organize electrocardiographic observations by field analysis methods. A mathematical process has thus been introduced to correlate calculated spatial orientations of the electromotive forces generated by the heart with clinical and pathologic observations. Whether a true orientation might be of much greater value than a calculated semi-empiric orientation remains to be established, but a quantitative estimation of the deviation of calculated orientation from

true orientation will necessitate careful consideration of the relative resistivities and spatial arrangements of the various tissues surrounding the heart.

If major inhomogeneities of resistance of the tissues surrounding the heart were found to be present, electrocardiographic interpretation of local abnormalities of myocardial electrical generation might best be studied by the application of circuit analysis, rather than of field analysis methods.

Summary

The validity of the field concept of electrocardiographic theory as currently employed is dependent upon the assumption that various body tissues are approximately uniform in electrical conductivity. The estimation of the relative resistivities of tissues has long been a subject of investigation. In this paper, the status of the problem is brought up to date.

1. Various indirect approaches to the problem are discussed. The reasons are indicated for the inconclusive and unconvincing nature of the results.

2. The complexity of the problem of direct measurement is suggested in an outline of the progressive intricacy of electrical measurements step-by-step from wire, to electrolyte in solution, to excised tissue, to tissue in situ.

3. Measurements of the resistivity of excised tissues are briefly reviewed. A wide range of variation has been found. These results cannot be directly applied to the problem of the resistivity of tissues in situ, and hence are of uncertain value in the study of electrocardiographic theory.

4. In the only quantitative study of electrical conductivity of individual tissues in situ, Kaufman and Johnston concluded that inconsequential error results from considering the tissues surrounding the heart uniform with respect to conductivity. We believe that acceptance of these conclusions must be reserved because: (a) From an analysis of the reported resistivity measurements, one finds a variation which would be expected to influence considerably the distribution of potential in an electrical field; and the degree of uniformity necessary "for practical purposes" has not yet been established. (b) From an analysis of their experiment, including actual repetition and extension of certain of the crucial procedures, the reported figures for resistivity have included a large, unknown quantity derived from the electrode system as a result of polarization.

5. It is concluded that: (a) An accurate, quantitative measurement of the resistivity of various individual body tissues in situ has not yet been made. (b) Dependent upon the magnitude of inhomogeneity found, extensive modification of field theory as currently applied to electrocardiography may be necessary. Calculated spatial orientations of the electromotive forces generated by the heart, deviating from true orientations to an unknown degree, may be usefully employed on a semi-empiric basis when correlated with clinical and pathologic observations. True orientations will require carefuly consideration of the resistivities and spatial orientations of the various tissues surrounding the heart. (c) Inhomogeneity, if sufficient in magnitude, could prove to be advantageous to electrocardiographic interpretation by providing the conditions necessary for the study of localized abnormalities of electrical generation by the myocardium. If so, circuit analysis methods might be more practical than field analysis methods.

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The general organization of the problem and preparation of the section on technical aspects of tissue resistivity measurement were primarily the responsibility of the senior author (J.M.B.). The second author (H.S.) was directly responsible for the planning and execution of the experiments concerned with polarization. In these he was assisted by J.M.B. and J.H.H. He was also responsible for the critical theoretic analysis of the whole problem of polarization. The orientation of the problem of tissue resistivity to electrocardiography was primarily the responsibility of C.F.K. All authors shared in preparation and editing of the manuscript.

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Localized Interlobar Effusion in Congestive Heart Failure

Vanishing Tumor of the Lung

By WILLIAM I. GEFTER, M.D., KATHARINE R. BOUCOT, M.D., AND E. WAYNE MARSHALL, M.D.

Four illustrative cases of localized interlobar effusion as a manifestation of congestive heart failure are presented. The right transverse fissure was most often involved. The x-ray shadow was dense and variable in shape, frequently resembling a tumor mass, and consequently presented a diagnostic problem. Diagnosis was confirmed by demonstrating the disappearance of the "tumor" following diuresis and restoration of cardiac compensation. The disorder is apparently not rare.

VANISHING TUMOR of the lung is an appropriate designation for a localized transudative interlobar pleural fluid collection in congestive heart failure. It derives its name from its frequent resemblance to a tumor in the roentgenogram and from its tendency to vanish following mobilization of the fluid and effective diuresis.

Inasmuch as only about 18 cases[1–14] have been reported in the literature, one would presume that the lesion is rare. Therefore, we were surprised to have encountered 6 cases in the past year, 4 of which we are reporting herewith. Doubt as to the rarity of the disorder was confirmed by talks with radiologists, who were aware of the entity; it seems generally unfamiliar to internists. The frequency of vanishing tumors of the lung must be greater than reported data indicate. At the Philadelphia General Hospital where admissions run about 25,000 per year, one of the radiologists recalls about 10 such cases over the past 15 years.[15]

The prerequisites for the development of a vanishing tumor of the lung are (1) congestive heart failure and, probably, (2) obliterative pleuritis. The degree of the heart failure may vary from mild to severe. In Laufer's[13] case the interlobar effusion at first was the only manifestation of heart failure. The etiology of the heart disease may be of any type (table 1). Of the 18 cases in the literature, the type of heart disease was arteriosclerotic in 7, hypertensive in 3, rheumatic in 2, syphilitic in 1, thyrotoxic in 1; the etiology was not stated in 4 instances. Three of our 4 cases had hypertensive cardiovascular disease; the fourth had arteriosclerotic disease.

Obliterative pleuritis prevents accumulation of fluid in the free pleural space so that the interlobar collection is visible. In each of the 3 autopsied cases previously reported[3, 5, 7] there was obliteration of the right pleural cavity except for the fissure between the upper and middle lobes which contained localized fluid. In Austrian's case a fluid collection was also present in the right oblique fissure.[7] The simultaneous loculation of fluid in the pleural cavity as well as in the interlobar space is evidence favoring the existence of pleural symphysis. Against the theory that obliterative pleuritis must be present are the findings in Laufer's case[13] in which a collection of fluid in the right transverse fissure disappeared following treatment of the heart failure. Five months later the patient developed bilateral pleural effusions. Thus, the pleural cavity could not have been obliterated at the time the interlobar effusion was present.

In most of the reported cases there was no adequate history to account for the obliterative pleuritis. Flattened diaphragms and obliterated costophrenic angles are not at all uncommon in mass surveys. These may be interpreted as evidence of old pleurisy with probable pleural symphysis. A significant percentage of such individuals when interviewed have no recollection of an episode of acute

From The Philadelphia Tuberculosis & Health Association, Hospital of the Woman's Medical College of Pennsylvania, Philadelphia General Hospital, and Pennsylvania Hospital.

pleurisy. It might also be noted that phthisiologists are familiar, from unsuccessful attempts to induce pneumothorax, with the fact that chest x-ray films may reveal no evidence of pleurisy despite pleural symphysis.

Case Reports

Case 1. F. R. H., a 53 year old white man, was well until February, 1948, when he suddenly became dyspneic while at work as a railroad trainman. He was hospitalized for three weeks and was told he had "bronchial trouble." X-ray examination showed his chest to be normal. He returned to work and remained relatively asymptomatic except for progressive exertional dyspnea. In September, 1948, he again developed sudden dyspnea which was promptly relieved by an injection administered by his physician. Since then he had had a productive cough, especially in the morning. In October, 1948, he had a recurrent attack of dyspnea associated for the first time with wheezing. An electrocardiogram is reported to have indicated changes possibly due to an old anterior myocardial infarction. Digitalis was then prescribed by his physician and he improved slightly. His dyspnea and wheezing increased thereafter until he was no longer able to work. He remained under treatment for "asthma" but, by December, 1948, he had lost 10 pounds over a 3 month period. On his own initiative he visited the survey unit at the Philadelphia Tuberculosis and Health Association where a photofluorogram was interpreted as showing a tumor or cyst of the right lung. These findings were confirmed by large films taken Dec. 7, 1948 (fig. 1*A*). Immediate hospitalization was recommended.

Table 1.—*Underlying Causes of Heart Disease in Vanishing Tumor of the Lung*

Etiology	Cases	
	Reported	Presented
Arteriosclerotic	7	1
Hypertensive	3	3
Rheumatic	2	—
Syphilitic	1	—
Thyrotoxic	1	—
Undetermined	4	—
Total	18	4

Table 2.—*Sites of Involvement in Vanishing Tumor of the Lung*

Site	Cases	
	18 Reported	4 Presented
Right transverse fissure	18	4
Right oblique fissure	2	1
Lateral chest wall	1	1
Paramediastinal	1	—
Pericardial	1	—

On Jan. 5, 1949 the patient was admitted to the Hospital of the Woman's Medical College. X-ray examination on the same day (fig. 1*B*) revealed a mass in the right lung but in a different location from that reported on Dec. 7, 1948. An electrocardiogram taken Jan. 6, 1949 disclosed a heart rate of 86 with frequent premature ventricular contractions originating in different foci. The QRS complexes were low in voltage in Lead II and inverted in Lead III. The T waves were inverted in Leads I, CF_4, CF_5 and CF_6, and diphasic in Lead II. The left axis deviation and the T-wave changes suggested myocardial damage secondary to hypertension. Because the patient had been admitted as a carcinoma suspect, bronchoscopy had been ordered. On Jan. 7, 1949 endoscopy revealed a congested tracheobronchial mucosa. Bronchial secretions were normal in cytology and on culture. Routine blood count, blood sugar, blood urea nitrogen and urinalysis were not remarkable. On Jan. 8, 1949 the admission chest film was compared with the film taken prior to admission. The change in the position of the "mass" was recognized at once as the shift of localized fluid so that a diagnosis of "vanishing tumor of the lung" was made.

Cardiac consultation revealed dyspnea at rest, slight orthopnea, faint cyanosis, and bilateral engorgement of the neck veins in the semirecumbent position. The heart was enlarged, the rate was rapid and increased with slight exertion. Frequent premature ventricular contractions were present. The aortic second sound was accentuated. At the mitral area there was a blowing systolic murmur. A gallop rhythm was present. Blood pressure was 150/110. Bilateral basal rales were present. The liver was tender and the edge was palpable 3 fingerbreadths below the costal margin in the midclavicular line. There was no ascites or edema. The patient had hypertensive heart disease with congestive failure and it was agreed that the pulmonary "masses" represented interlobar fluid collections. The previous attacks of dyspnea and bronchospasm were interpreted as episodes of left ventricular failure. A salt-poor diet and continued digitalis were prescribed. (The patient had been taking 0.1 Gm. of digitalis daily). The patient was given 2.0 cc. of Mercuhydrin intramuscularly as a therapeutic measure. Two days later, on Jan. 10, 1949, the patient was remarkably improved. He was clinically free of failure and the gallop rhythm had disappeared. Re-examination of his chest (fig. 1*C*) revealed marked absorption of the interlobar fluid localized in the fissures between the right middle and upper, and middle and lower

lobes. On Jan. 11, 1949 he was totally asymptomatic. He was discharged from the hospital on Jan. 14, 1949.

April 5, 1949 the patient was discharged. Subsequent fluoroscopic examinations of his chest have been negative.

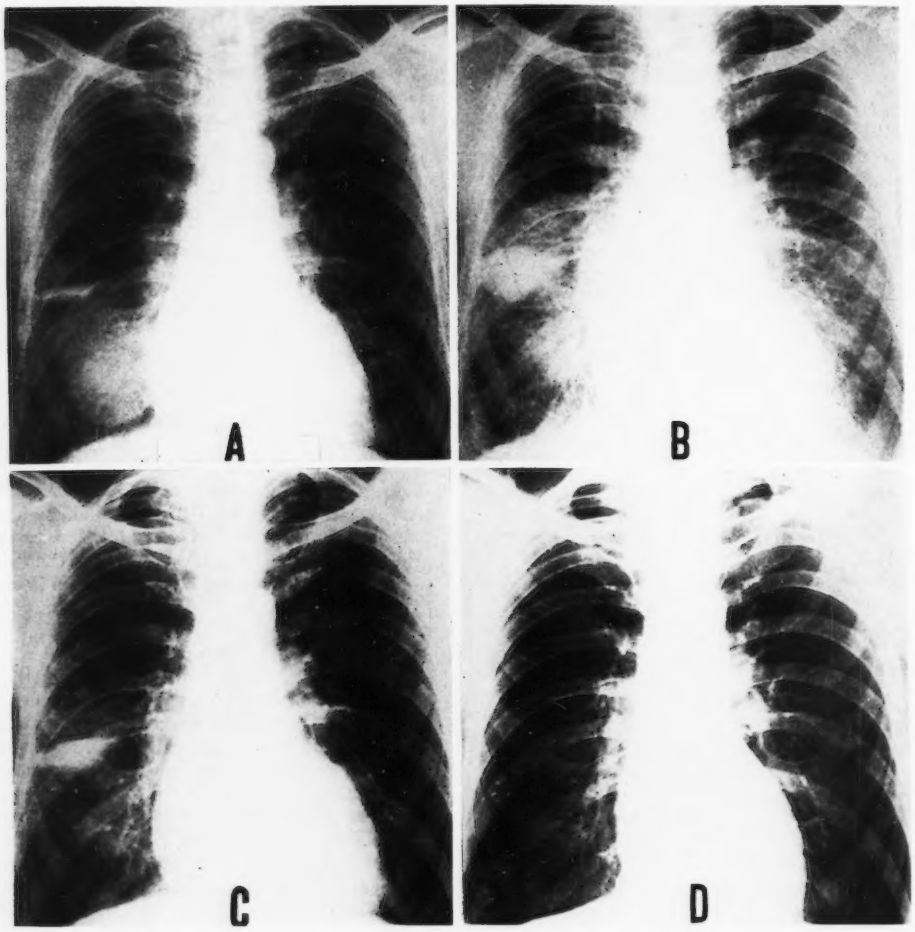

FIG. 1. Case 1. *A*. December 7, 1948. Large round discrete density in lower right lung field interpreted as tumor or cyst. A small wedge-shaped shadow lies above the mass. There are interlobar effusions in both oblique and transverse fissures.

B. January 5, 1949. The "mass" has "shifted." The heart is enlarged and pulmonary congestion is present. Alteration in the densities made obvious the diagnosis of vanishing tumor of the lung.

C. January 10, 1949. Two days following mercurial diuretic. Considerably less fluid in the interlobar fissures. In the anteroposterior view the collection in the oblique fissure is barely visible.

D. March 30, 1949. Negative chest except for slightly thickened right oblique interlobar fissure which was only visible in lateral view.

He remained perfectly well and was back at work until March 28, 1949 when he developed an acute tracheobronchitis. The readmission chest film of March 29 (fig. 1*D*) was negative except for slight thickening of the right oblique interlobar fissure. On

Had this patient not sought an x-ray examination of his chest voluntarily, the localized interlobar effusions might never have been discovered. He had become progressively worse

over a period of 10 months despite medical attendance. The diagnosis of a mass was made entirely on the basis of the survey photofluorogram without the advantage of an interview with the patient. Because of the discouraging results in bronchogenic carcinoma it is right and proper that patients with survey films read as "suspect neoplasm" should be hurried to the hospital as medical emergencies. This is the only proved case of vanishing tumor encountered in some 250,000 photofluorograms at the Philadelphia Tuberculosis and Health Association over a five-year period. As a result of the mistaken impression, however, this patient was subjected to bronchoscopy needlessly. Had the possibility of a localized interlobar fluid collection been kept in mind, bronchoscopy would have been postponed until after a cardiac evaluation. The diagnosis was first suspected when comparison films made one month apart showed a change in the location of the "tumor." Suspicion was confirmed by the findings of underlying congestive heart failure and proved conclusively by striking decrease in the size of the densities following diuresis. With continued adequate therapy there has been no recurrence of the heart failure.

Case 2. J. McG., a 49 year old white man, was admitted to the Philadelphia General Hospital, Medical Service of Dr. W. G. Leaman, Jr., on May 31, 1949 with the chief complaint of "shortness of breath." For the past three years he had had increasingly severe exertional dyspnea. In the last 3 months frequent attacks of paroxysmal nocturnal dyspnea had occurred. Two months ago he had developed a persistent irritating cough productive of small amounts of whitish material. Ankle edema first appeared four years ago, recurred intermittently, but had increased in severity during the four months prior to hospitalization. For the week before admission the ankles and legs had remained swollen. Recently the patient had noticed occasional chest pain momentarily during exertion.

Past history and systemic review were noncontributory except that the patient had been a moderate user of alcohol for many years. Following the recent death of his wife, his drinking had become excessive.

Physical examination revealed a fairly well developed, well nourished man in no acute respiratory distress. The temperature was 98.6 F., pulse 92 (totally irregular), respirations 28 and blood pressure 140/90. The veins of the neck were markedly distended but not pulsating. The chest was moderately emphysematous and breathing was asthmatic throughout. At both bases there were crepitant rales and decreased resonance. The apex of the heart was slightly beyond the midclavicular line in the fifth intercostal space by percussion. The cardiac rhythm was irregular and the rate rapid with a pulse deficit of about 18 beats per minute. The liver was tender and the edge was felt 11.0 cm. below the rib margin. There were no other remarkable abdominal findings. The extremities showed three plus pitting edema to the knees.

Laboratory studies were: hemoglobin 15.9 grams; white blood cells 7,350, with a normal differential count; blood sugar 125 mg. per cent; blood urea nitrogen 17 mg. per cent; normal urinalysis with specific gravity 1.016; blood serologic test for syphilis negative. The electrocardiogram showed auricular fibrillation with a ventricular response of 140. X-ray films of chest made on June 2, 1949 (fig. 2*A*) revealed generalized cardiac enlargement and bilateral hilar vascular engorgement with a rounded homogeneous density in the outer portion of the middle third of the right lung; a lateral view was not obtained. The shadow was regarded as a localized effusion in the transverse interlobar fissure.

The patient was given 1.6 mg. of digitoxin orally in divided doses and 2 cc. of Thiomerin subcutaneously during the first 24 hours, following which the apical rate declined to 100 beats per minute. On the following day he was given 0.4 mg. of digitoxin and 0.2 mg. thereafter daily. He also received ammonium chloride by mouth and an additional injection of Thiomerin. By June 6 the chest rales, leg edema, and liver engorgement had disappeared. The apical rate remained about 88 per minute after June 4.

On June 7, x-ray examination (fig. 2*B*) revealed almost complete disappearance of the homogeneous density reported 5 days previously in the middle third of the right lung field. There remained only slight interlobar pleural thickening. The cardiac silhouette was unchanged.

On June 9, 1949 the patient was discharged to the Heart Clinic on a salt-free diet and a maintenance digitoxin dosage of 0.2 mg. daily.

Because of the interest in vanishing tumors due to experience with the previous case, the diagnosis was made easily in this instance. As expected, the interlobar fluid collection vanished promptly following adequate diuretic response.

Case 3. J. S., a 64 year old white woman, attended the Benjamin Franklin Clinic of the Pennsylvania Hospital on July 15, 1949. For the previous year she had had exertional dyspnea, a choking sensation in her throat, anorexia, abdominal bloating, and ankle edema. Despite the swelling of her legs she had lost 30 pounds in weight and complained of

fatigue. She also had nocturia several times nightly. In 1926 she had had a caesarean section and in 1932 a cholecystostomy with removal of a gall stone.

On examination the patient was slightly obese. The mucous membranes were somewhat pallid and the lips mildly cyanosed. The neck veins were moderately distended in the sitting position. There was slightly diminished expansion at the base of the right chest, dullness to percussion and a few scattered rales were present in this area and low in the right axilla. The heart was enlarged to the left anterior axillary line. The rhythm was grossly irregular and the ventricular rate was 112. No murmurs were heard. The blood pressure was 110/60. The liver edge was palpable four fingerbreadths below the costal margin. There was pitting edema of both lower limbs.

Fluoroscopically the right diaphragm was slightly restricted in motion and adhesions were present at the right costophrenic angle. An area of thickened pleura and loculated fluid was present along the right midlateral chest wall. Above the right diaphragm there was a circular area of density thought to be in the transverse interlobar fissure. The right hilum and ascending arch of the aorta were prominent. The heart was rather enlarged to the left and right.

Blood count, serology and urinalysis were normal. Sedimentation rate was 20 mm. in one hour and the total protein was 5.8 grams.

Electrocardiogram revealed auricular fibrillation with a ventricular rate of 96, left axis deviation, low amplitude of QRS complexes and T waves in all leads. The changes were considered to be related to myocardial damage secondary to coronary disease.

X-ray examination of the chest on July 20, 1949 (fig. 3*A*) showed a normal left lung. In the right midlung field there was a rounded shadow at the level of the eighth rib posteriorly in the mid-scapular line. In the lateral view this area of density was well forward and at the site of the interlobar fissure. There was an area of encapsulated fluid in the pleural cavity along the right lateral chest wall from the second to the seventh ribs in the midaxillary line. The right costophrenic angle was obliterated and the right diaphragm was not smooth. The lower lobes showed increased trunk shadows. The radiologic interpretation was encapsulated empyema following some lung infection.

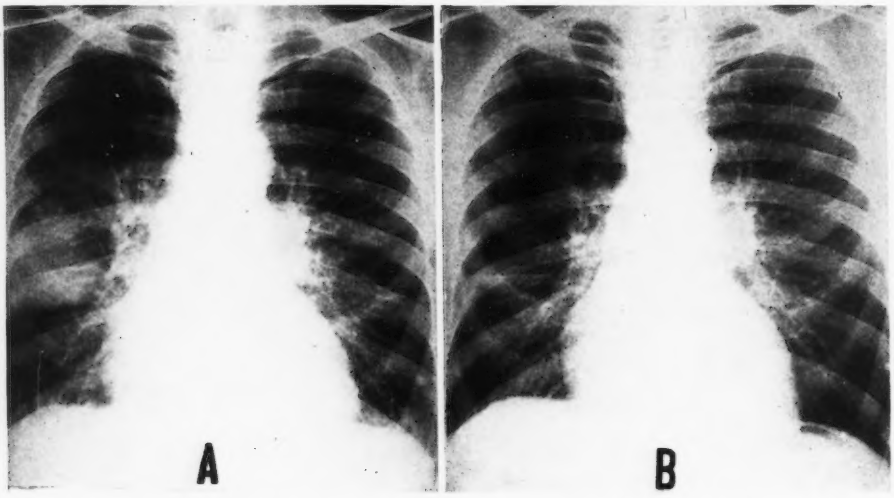

FIG. 2. Case 2. *A*. June 2, 1949. Round density in right mid-lung. Cardiac enlargement and hilar congestion. The shadow was regarded as a localized effusion in the transverse interlobar fissure.
B. June 7, 1949. Five days after diuretic therapy. The shadow has disappeard. There remains only a thickened transverse interlobar fissure seen only in the anteroposterior view.

The clinical diagnosis was arteriosclerotic heart disease, cardiac enlargement, auricular fibrillation, Class 4 D, congestive heart failure manifested by loculated pleural effusion and loculated interlobar pleural effusion.

The patient was admitted to the Pennsylvania Hospital on August 10, 1949. She was digitalized over a three day period and maintained thereafter on digitalis, 0.1 Gm. daily. She received 2.0 cc. of Mercuhydrin intramuscularly every day and was given a course of ammonium chloride. She was placed on a salt-poor diet. After one week she lost 7 pounds, the rales disappeared from the right base and her ventricular rate slowed to about 75. The liver decreased in size and the leg edema practically dis-

appeared. Subjectively she improved greatly and her dyspnea lessened. X-ray films of the chest made Aug. 19, 1949 (fig. 3*B*), eight days after onset of therapy, showed marked improvement. The loculated fluid along the right lateral chest wall had disappeared. There was marked clearing of the interlobar effusion. The changes in the diaphragmatic sulcus decreased.

She was discharged on Aug. 19, 1949 to the care of her family physician and has apparently been well.

*Case 4.** J. S., a 67 year old white man was admitted to the Montgomery County Hospital, Norristown, Pa. on November 16, 1945, with a history of exertional dyspnea and ankle edema of five weeks' duration. A year previously he had a prostatectomy. On examination his blood pressure was 160/80; the

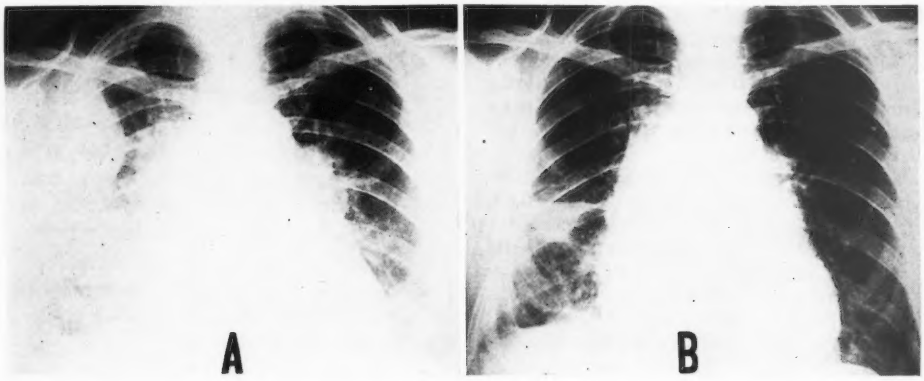

FIG. 3. Case 3. *A*. July 20, 1949. Round dense shadow in right mid-lung. Large homogeneous density along the right lateral chest wall with obliteration of costophrenic angle. Cardiac enlargement. The radiologist's impression was encapsulated empyema following lung infection.

B. August 19, 1949. Eight days following institution of diuresis. The encapsulated fluid along the chest wall has vanished. The interlobar effusion has cleared markedly. Cardiac enlargement persists.

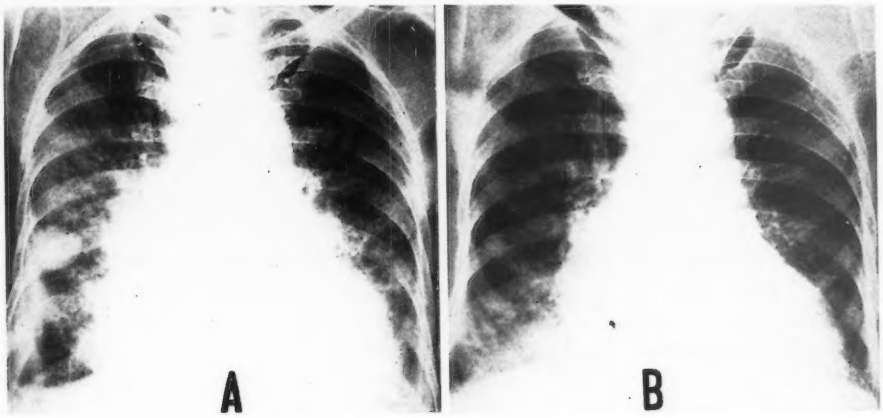

FIG. 4. Case 4. *A*. November 17, 1945. Round dense shadow in right mid-lung. Density along lower right lateral chest wall. Cardiac enlargement and pulmonary congestion. Radiologic interpretation was metastatic neoplasm and congestive heart failure.

B. December 3, 1945. The round shadow has disappeared following treatment of the congestive failure. Cardiac enlargement and congestion at the right base persist.

* We are grateful to Dr. Louis Cohen for allowing us to report this case to which he called the attention of one of us in 1945. It was the first patient with vanishing tumor of the lung encountered by any of the authors.

pulse rate was 120; his neck veins were prominent; there were bilateral basal pulmonary rales; the heart was enlarged to the anterior axillary line and a systolic murmur was heard in the mitral area; the cardiac rate was rapid and the rhythm irregular; the liver was palpable one and a half fingerbreadths below the costal margin; there was slight edema of both ankles. He was afebrile and his blood count was normal. Electrocardiogram showed auricular fibrillation, left axis deviation and T-wave changes indicating left ventricular strain and severe myocardial damage. On admission he was placed on digitalis, 0.1 Gm. twice daily, ammonium chloride, 0.5 Gm. four times a day, and aminophylline, 0.240 Gm. intravenously daily. On November 17, the day following admission, a roentgenogram of his chest (fig. 4*A*) was interpreted as probable metastatic neoplasm with myocardial failure. Upon re-examination on December 3 (fig. 4*B*) the pulmonary mass had disappeared. He was discharged from the hospital, improved.

The radiologic diagnosis of empyema was discounted by the clinician on the basis of congestive heart failure which made it probable that the densities in the right lung represented localized effusions secondary to failure. The excellent response following diuresis confirmed this suspicion. The disappearance of the encapsulated effusion along the chest wall prior to that of the interlobar collection of fluid is reminiscent of the behavior of the fluid in DiMaio's case.[14] According to Schwedel[16] the fluid in the interlobar space disappears before that present in the general pleural cavity.

Discussion

Hydrothorax in congestive heart failure is predominantly right-sided[17] and the majority of the reported cases of vanishing tumor of the lung are also right-sided. The transverse fissure between the right upper and middle lobes was involved in every reviewed case (table 2). This was true in our 4 cases as well. In Kiser's[4] case there was coexisting pericardial effusion which disappeared along with the interlobar fluid following diuresis. Stein and Schwedel[9] reported a case with a collection of fluid in the fissure of an azygos lobe although there was also free fluid in the pleural cavity. The only reported cases with more than one localized effusion are those of Austrian[7] and Roesler[11] in which fluid was present simultaneously in the right transverse and oblique fissures and that of DiMaio[14] in which, in addition to a collection in the right transverse fissure, there was a localized fluid mass in the right upper lateral portion of the pleural cavity and in the anterior superior paramediastinal space. In one of our cases (case 1) there were localized fluid collections in the right transverse and oblique interlobar fissures and in two others (cases 3 and 4) the right transverse fissure and right lateral chest wall were involved at the same time. One of the cases recorded by Stein and Schwedel[9] had thickening of the left oblique fissure. In a case known to us, but not being reported because of lack of adequate clinical details, there was fluid in the left oblique fissure as well as in the right transverse fissure.

Generally the interlobar pleural effusion is not demonstrable by physical examination although other evidence of congestive failure is easily obtained. The amount of fluid is usually small, deeply seated and surrounded by lung substance. The diagnosis is made by fluoroscopy or from the roentgenogram. The appearance is most often that of a well defined homogeneous density, usually in the right lung, occupying especially the transverse, but occasionally the oblique interlobar fissures. In the roentgenogram the shadow may assume round, oval, spindle, semilunar, wedge or linear shapes depending upon the volume and position of the fluid, the projection angle and the amount of surrounding pulmonary compression.[18] Fluid in the transverse fissure is best observed in the anteroposterior view but fluid in the oblique fissure is best visualized in the lateral view of the chest.[9] Case 1 illustrated this well. Aspiration for diagnostic purposes is contraindicated because of the possibility of inducing hemorrhage and/or pneumothorax. The therapeutic response to diuresis is confirmatory and usually prompt. When congestive failure recurs the fluid may return to the original localized site. In Stewart's[3] patient the interlobar effusion in the right transverse fissure disappeared three times only to recur a fourth time prior to the death of the patient.

The differential diagnosis must include all the causes of interlobar effusion: pneumonia, tuberculosis, malignancy, infarction, together

with more rare entities. There must be excluded conditions resembling interlobar fluid collections, such as empyema and abscess, primary and metastatic neoplasm, cyst, arteriovenous aneurysm. Robbins and Hale[19] point out that atelectasis of the right middle lobe should not be confused with interlobar effusion. None of these can be influenced by diuresis as can a localized interlobar effusion.

Summary

Four cases are reported of so-called "vanishing tumor of the lung" (localized interlobar pleural effusion in congestive heart failure) and the subject is reviewed.

It is suggested that the condition may be more common than the literature indicates.

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Effect of Khellin on Coronary Artery Insufficiency as Evaluated by Electrocardiographic Tests

By MAURICE M. BEST, M.D. AND WALTER S. COE, M.D.

The effectiveness of khellin in 9 patients with angina pectoris was evaluated electrocardiographically by means of the exercise tolerance, anoxemia and ergonovine tests. Normalization occurred in the majority of the previously abnormal tests following khellin therapy. A beneficial effect was noted on symptoms accompanied by a reduction in nitroglycerin requirement. Mild toxicity, as a result of khellin therapy, was observed in 3 cases.

KHELLIN is a crystalline substance isolated from the seeds of the plant *Ammi visnaga*, which grows abundantly in the Eastern Mediterranean region. It has been used for centuries for the treatment of conditions characterized by spasm of smooth musculature. The drug has been shown by Samaan[1] to relax smooth muscle by direct action on the muscle fibers.

The pharmacologic action of khellin on the coronary circulation has been studied by Anrep, Barsaum, Kenawy, and Misrahy.[2] In heart-lung preparations they observed that concentrations of the order of 1 in 200,000 resulted in increases in coronary blood flow of 3 to 4 times the initial volume. In dogs they demonstrated the action of khellin in therapeutic doses to be largely selective on the coronary vessels since action on systemic blood vessels and blood pressure is negligible.

Clinical evaluation of the drug in angina pectoris was recently reported by Anrep and his co-workers.[3] In a series of 250 cases, 56 per cent showed good subjective improvement, 34 per cent showed moderate improvement and 10 per cent were classified as failures. Some of their patients were studied objectively by utilizing the effect of exercise on the electrocardiogram following intramuscular injection of khellin.

From the Institute for Medical Research and Department of Medicine, University of Louisville School of Medicine, Louisville, Kentucky.

METHOD AND TECHNIC

Selection of Patients. The 9 patients selected for this study fulfilled the following criteria: history of classic angina pectoris on exertion; no evidence of congestive heart failure, hyperthyroidism or anemia; no recent myocardial infarction; and at least 1 of 3 electrocardiographic tests for coronary insufficiency positive.

Medication. All patients were observed through at least a one-month control period. They then received khellin,* 50 mg. (one tablet) orally three times a day for a period ranging from two to four weeks. All patients received one placebo tablet three times a day for at least one month. Four patients received these tablets before and five at the completion of khellin therapy. The placebo tablets were identical in appearance and indistinguishable in taste from the khellin tablets. Daily nitroglycerin consumption was recorded throughout each period. The observer who recorded symptomatic response and nitroglycerin consumption was unaware which type of tablet the patient was receiving. All patients remained ambulatory and continued their usual activities throughout the periods of study.

Electrocardiographic Evaluation. The following tests were done before treatment, at completion of khellin therapy, and following placebo administration:

* The khellin used in these studies was supplied through the courtesy of Merck and Company, Rahway, New Jersey.

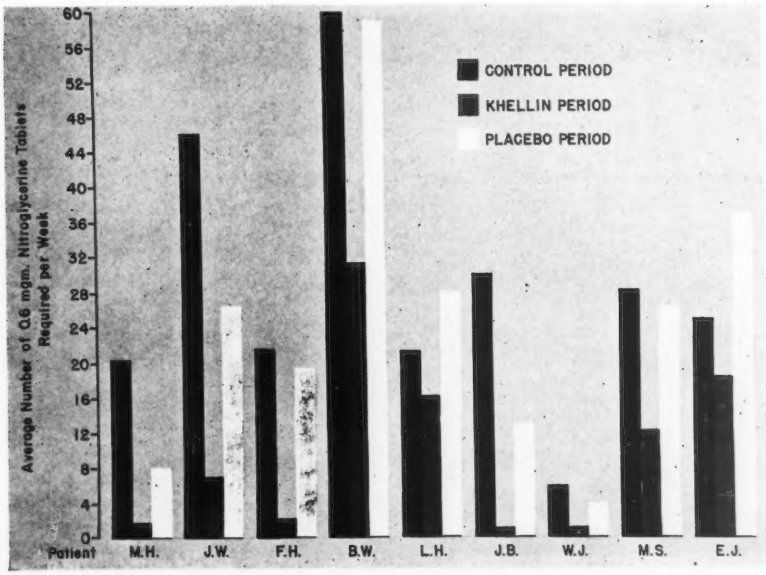

FIG. 1. Effect of khellin on nitroglycerin requirement.

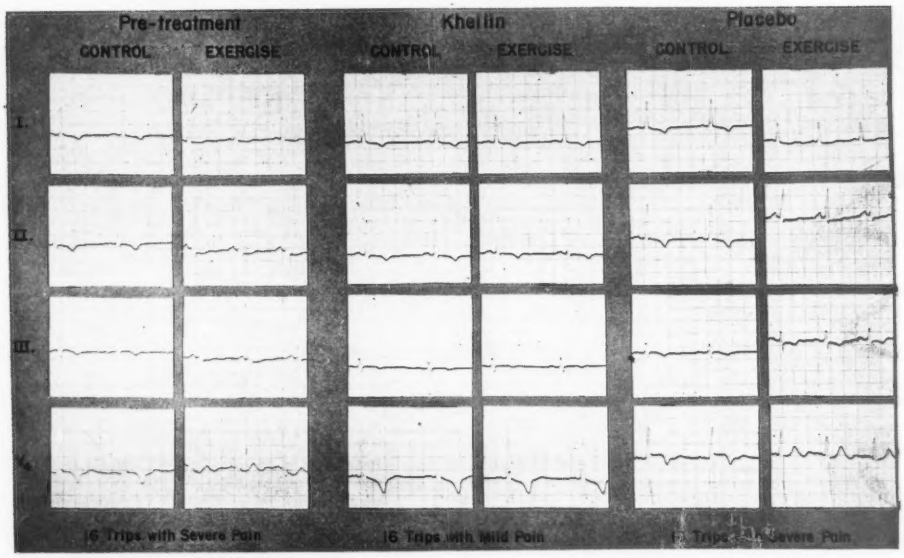

FIG. 2. Patient M. S., 65 years of age. Five-year history of angina pectoris. Exercise tolerance test. Pretreatment electrocardiograms show depression of RS-T segment in Leads II and III; T waves in Leads I, II, III and V_4 become upright. No changes in tracings during khellin period. During placebo period the form of the pretreatment tests has been resumed.

(1) Exercise tolerance test, as described by Master and associates[4] with graded exercise on standard steps. The patients rested 15 minutes and then performed the standard amount of exercise as indicated by tables based on sex, age and weight, and completed the de-

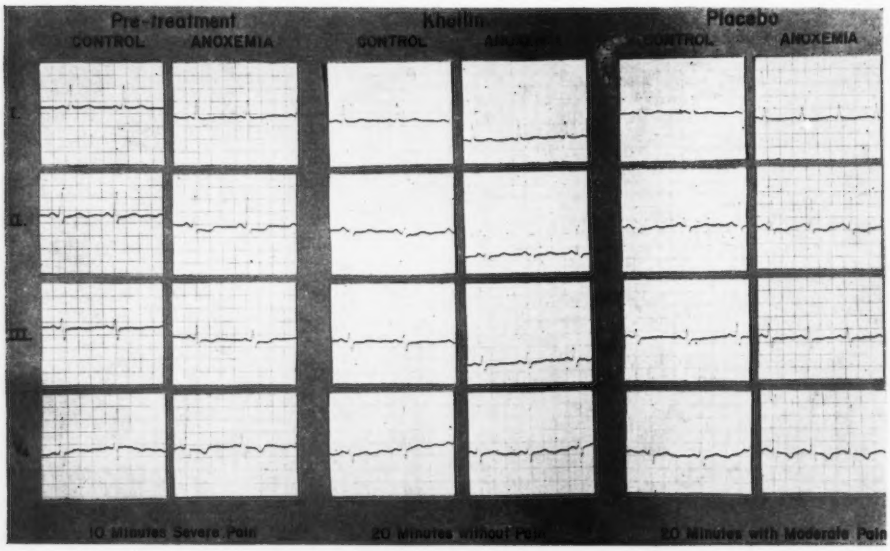

FIG. 3. Patient M. H., 56 years of age. Three-year history of angina pectoris. Anoxemia test. Pre-treatment electrocardiograms show depression of RS-T segment in Leads II and III; T wave inversion in Leads I, II, III and V_4. No significant changes in tracing during khellin period. Placebo period shows inversion of T waves in Leads I, II and V_4.

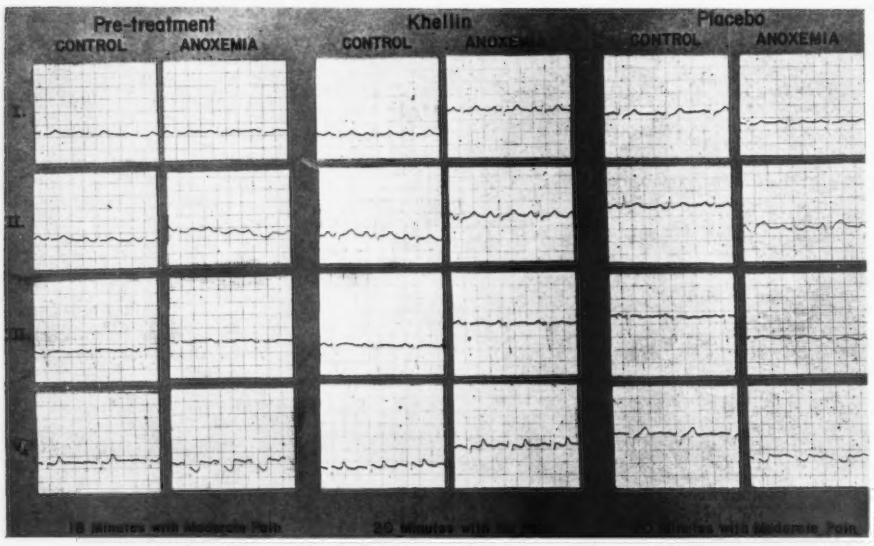

FIG. 4. Patient J. B., 50 years of age. Three-year history of angina pectoris. Anoxemia test. Pre-treatment electrocardiograms show depression of RS-T segment and inversion of T wave in Lead V_4. No significant changes in tracings during khellin period. Placebo period shows ventricular premature contractions in Lead II and depression of RS-T segment in Lead V_4 with development of a diphasic T wave.

termined exercise in one and one half minutes. Electrocardiograms consisting of Leads I, II, III, and V_4 were recorded before exertion. These were repeated immediately on cessation of exercise and at intervals of 3, 5, and 8 minutes thereafter. In the event of pain, an immediate electrocardiogram was recorded and nitroglycerin, 0.43 mg. was given.

Criteria for a positive test consisted of a depression of the RS-T junction of at least 1 mm. in any lead, conversion of an upright T wave to an isoelectric or inverted T in Leads I, II,

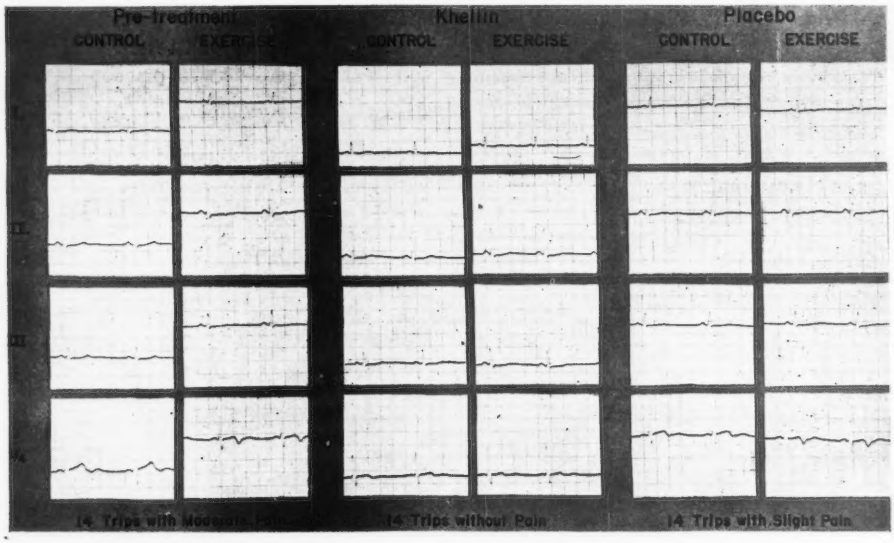

FIG. 5. Patient W. J., 81 years of age. Ten-year history of angina pectoris. Exercise tolerance test. Pretreatment electrocardiograms show inversion of T waves in Lead I, II and V_4. No significant changes in tracing during khellin period. Placebo period shows inversion of T waves in Leads I, II and V_4.

TABLE 1.—*Effect of Khellin on Electrocardiographic Tests for Coronary Artery Insufficiency*

Patient	Exercise Tolerance Test		Anoxemia Test		Ergonovine Test	
	Control*	Khellin	Control*	Khellin	Control*	Khellin
M. H.	—	—	+	—	—	—
J. W.	+	—	—	—	—	—
F. H.	+	—	—	—	—	—
B. W.	+	—	+	—	+	0
L. H.	+	+	0	0	0	0
J. B.	+	—	+	—	—	—
W. J.	+	—	—	—	—	—
M. S.	+	—	—	—	—	—
E. J.	+	+	+	0	+	—

\+ Positive test.
— Negative test.
0 Test not performed.
* Post-treatment placebo results were identical with pretreatment control studies.

or V_4; or conversely the conversion of an inverted T wave to an upright T wave in these leads. The appearance of multifocal ventricular premature contractions was also considered an abnormal response.

(2) Anoxemia test was performed according to the method of Levy and his co-workers.[5] A mixture of 10 per cent oxygen and 90 per cent nitrogen was administered through a gas machine equipped with a flutter valve so that no rebreathing occurred. Periodic analysis by the method of Haldane of the gas mixture revealed the oxygen content to remain constant at 10 ± .02 per cent. By means of a simple push button 100 per cent oxygen could be immediately substituted for the reduced oxygen mixture. A control electrocardiogram consisting of Leads I, II, III, and V_4 was obtained initially.

The oxygen-nitrogen mixture was then given for 20 minutes. Electrocardiograms were recorded at intervals of 5 minutes during the period of reduced oxygen administration and for 15 minutes thereafter. In the event of pain an immediate electrocardiogram was recorded and 100 per cent oxygen administered.

Criteria for a positive test were similar to those of Levy[6]: the sum of the RS-T deviations in all leads totals at least 3 mm., or a reversal in the direction of the T wave in Leads I and V_4 if accompanied by RS-T depression of 1 mm. or more. We also considered the appearance of multifocal ventricular premature contractions to be an abnormal response.

(3) Ergonovine test was performed by the method of Stein.[7] Each patient was required to rest at least 20 minutes and a control electrocardiogram consisting of Leads I, II, III, and V_4 was recorded. Ergonovine maleate, 0.2 mg. was injected intravenously very slowly. The electrocardiogram was repeated immediately upon completion of the injection and at intervals of 3, 5, 15, and 30 minutes. Tablets of nitroglycerin, 0.43 mg., were given immediately if pain occurred.

The criteria for a positive test were depression of the RS-T segment of 1 mm. in any lead or conversion of an upright to an isoelectric or inverted T wave in Leads I, II, or V_4.

Results

Effect on Electrocardiographic Tests

The responses of the individual patients to the exercise tolerance, anoxemia and ergonovine tests are shown in table 1. Twenty-five tests were performed on the patients prior to treatment. Fourteen were positive. Ten (71.4 per cent) of these 14 positive tests reverted to negative following khellin therapy. Two tests remained positive and two tests were not repeated. One patient (B. W.) developed chaotic heart action following ergonovine and another patient (E. J.) refused to permit the anoxemia test to be repeated. All tests reverted to their pretreatment status with placebo therapy.

Occurrence of Pain during Testing

Precordial pain occurred during 17 (68 per cent) of the 25 pretreatment tests. Pain occurred on 4 (17.3 per cent) occasions during testing at the completion of khellin therapy. One patient (L. H.) experienced pain during the initial exercise tolerance test but had no pain on subsequent testing following khellin and placebo periods.

TABLE 2.—*Nine Patients with Coronary Artery Insufficiency Treated with Khellin*

Name	Age	Sex	Etiology	Duration of Angina	Duration of Khellin therapy	Symptomatic Improvement		Toxic Symptoms	
						Khellin	Placebo	Khellin	Placebo
M. H.	56	F	Arteriosclerotic	3 years	3 weeks	Yes	No	No	No
J. W.	52	M	Arteriosclerotic	4 years	4 weeks	Yes	No	No	No
F. H.	68	F	Arteriosclerotic	4 years	2 weeks	Yes	No	Yes	No
B. W.	65	M	Arteriosclerotic	6 years	2 weeks	Yes	No	Yes	Yes
L. H.	69	F	Arteriosclerotic	4 years	3 weeks	Yes	No	No	No
J. B.	50	M	Arteriosclerotic	3 years	2 weeks	Yes	Yes	No	No
W. J.	81	M	Arteriosclerotic	10 years	2 weeks	Yes	No	No	No
M. S.	65	F	Arteriosclerotic	5 years	2 weeks	Yes	No	Yes	No
E. J.	35	M	Syphilitic	3 years	2 weeks	No	No	No	No

Symptomatic Response

Eight patients noted an increase in exercise tolerance and a decrease in number and severity of anginal attacks while under treatment with khellin as contrasted to the control period, as shown in table 2. One patient reported symptomatic improvement with placebo tablets. The only patient (E. J.) in whom no subjective improvement occurred was thought to have syphilitic involvement of the coronary ostia.

Effect on Nitroglycerin Requirement

The effects of khellin and placebo tablets on average weekly nitroglycerin requirements as compared with those of the control period are summarized in figure 1.

Toxic Effects of Khellin

Nausea and vomiting were the only toxic effects noted. These occurred in 3 patients but were not so severe as to limit the use of the drug.

Discussion

Angina pectoris is generally thought to be due to a decreased coronary circulation which becomes inadequate when coronary filling is impaired by spasm or other factors or when cardiac work is increased.[8] It may be due to an inability of the arteriosclerotic arteries to dilate[9] but the presence of some degree of vasospasm is suggested by the classic response to the nitrites.

Direct measurement of coronary artery blood flow in man is not feasible. Estimation by means of coronary sinus catheterization following saturation of the blood by nitrous oxide as developed by Bing and his co-workers[10] is not applicable to problems of exercise tolerance. The electrocardiogram is probably the best means of evaluating the adequacy of coronary blood flow during periods of increased myocardial demand in man.

The conversion to a normal pattern of 71.4 per cent of the previously abnormal electrocardiographic tests of coronary insufficiency would indicate that khellin in the dosage used is helpful in preventing myocardial anoxia. The action may be that of vasodilatation of the coronary arteries as suggested by Anrep and associates and confirmed by their direct measurements in the dog.[2] In man with arteriosclerotic disease of the main coronary arteries, the drug may cause dilatation of collateral vessels sufficient to permit more blood to reach anoxic areas of the myocardium.

Subjective response to any drug in angina pectoris is difficult to evaluate. The majority of these patients during treatment with khellin noted an increase in ability to exercise without pain, used less nitroglycerin per week and had less pain during testing procedures as compared to the pretreatment control period. In only one patient was improvement sustained while on placebo tablets.

Limited supplies of available khellin restricted its dosage and the number of patients studied. It would seem that khellin may be an effective means of improving anoxia of the myocardium secondary to coronary artery disease. The drug warrants further experimental and clinical study.

Summary

(1) Of 14 abnormal electrocardiographic tests of coronary insufficiency obtained in 9 patients, 10 (71.4 per cent) reverted to normal with khellin therapy. This beneficial effect was not noted with placebo therapy.

(2) Eight of the 9 patients noticed an increase in exercise tolerance and a decrease in number and severity of anginal attacks while under khellin treatment.

(3) Nausea and vomiting of moderate severity occurred in 3 patients during khellin therapy.

(4) It would seem that khellin is of value in the treatment of angina pectoris.

Acknowledgments

The authors wish to express their appreciation to Morton L. Enelow, M. D., and the Department of Visual Education for their assistance in this study. We are also indebted to J. Murray Kinsman, M. D., and Herbert L. Clay, M. D., for their helpful suggestions.

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Some Characteristics of Certain Reflexes Which Modify the Circulation in Man

By LYSLE H. PETERSON, M.D.

Records are presented which have been obtained from man by direct intra-arterial catheterization and electrocardiography. These records have been selected (1) because they offer evidence for the validity of Starling's law in intact man and (2) because they demonstrate that when the heart is influenced by activity of the so-called "intrinsic" reflexes these manifestations of Starling's law are modified. It appears from these types of data that ventricular activity may be directly affected independently of influences upon the pacemakers of the heart.

INTRODUCTION

DURING THE past three to four years direct intra-arterial pressures have been obtained from almost 1000 persons. The method employed a tiny flexible tube inserted into an artery and then connected to a capacitance manometer and the pressure curves were recorded by means of an ink writer. This system permitted the observation of accurate records of the pulse contour over long periods of time without discomfort to the subject. Also, by observing the ink writer, changes in the circulation which follow stimuli could be at once identified. Such observations were carried on during a variety of conditions such as general or local anesthesia, surgery, many conditions of disease in its various stages and during certain physiologic and pharmacologic experiments.

While many of the periods of recording were not planned as such, in one way or another many of the conditions of certain classic physiologic experiments formerly performed on animals were hereby repeated on man. The results obtained on man, however, were by no means always concordant with the expectations from the classic animal experiments. This was especially true of the effects of carotid sinus stimulation upon the heart and circulation as well as other reflex effects arising from stimulation of the visceral mesentery. The evidence strongly suggests that such reflex pathways mediate activity which modifies the manifestation of Starling's law and which appear to affect the ventricle directly. These changes appear both with and without influence upon the pacemaker. Also, interesting observations have been made of the manner in which the pulse rate responds to circulatory alterations under certain conditions. It is the physiologic aspect of these observations which will be stressed in this presentation.

METHODS AND TYPE OF DATA

The method used for intra-arterial pressure measurements has been described elsewhere.[1] The fidelity of the system is such that accurate and linear recordings can be obtained from intra-arterial pressure changes to give true pulse contours.* This type of recording also eliminates the errors inherent in the Riva-Rocci method.

From the Department of Physiology, the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine, and the Department of Anesthesiology of the Hospital of the University of Pennsylvania, Philadelphia, Pa.

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* It is not the purpose of this paper to evoke a discussion of the validity of pulse pressures and contours as a representation of stroke volume. Suffice it to say that this author feels, as do others,[2-4] that the available evidence is such that, if one considers the contour as well as the pressures present in the accurately recorded arterial pulse wave, one is justified in using the data presented in the manner set forth in this paper. The available evidence indicates that the changes in pulse contour during its transmission from aorta to brachial artery are such that the criteria used with the aortic pulse may be used also for the brachial pulse.[5] In any event, the ballistocardiograph is the only other device or method allowing judgment of beat to beat changes in stroke volume. The type of data reported here could not have been obtained from direct Fick measurements.

Electrocardiograms have been obtained with a direct recording Sanborn Electrocardiograph.

Data and Discussion

I. *Manifestations of Starling's Law in Man.*

Figure 1 demonstrates typical effects following extra systoles. It should be noted that following the extra systole there is a period of prolonged diastole. The next beat is more forceful as is evidenced by an augmented pulse pressure and a contour indicating a larger stroke volume. We are justified in thinking that increased cardiac distention from the prolonged filling time caused the increased response in accord with Starling's law.

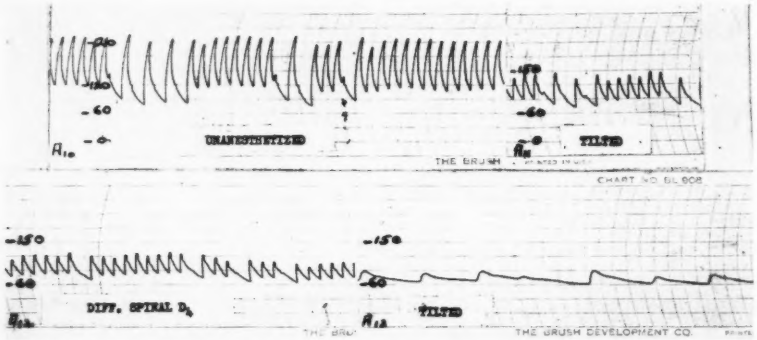

Fig. 1. Effects which follow extra systoles. These records were obtained from a 52 year old hypertensive patient. Upper left section obtained while patient was lying quietly on the tilting ballistocardiograph table. In this section 7 extra systoles which are followed by periods of prolonged diastole, then markedly stronger pulses, may be seen. These effects may also be seen in the upper right section which followed tilting to 70°, head up. The patient was then given a differential spinal anesthesia to a sensory level of D-4. Note that at all pressure levels a prolonged diastolic period is followed by a stronger contraction. It may also be noted that the pulse rate does not accelerate following the hypotension produced by differential anesthesia in this patient. In this case it may also be seen that there is not a marked alteration in the slopes of the pulse curves. All vertical lines represent 1 second except in the lower right section where the paper speed was 25 mm./second, i.e. each vertical line represents 0.20 second.

Although the records shown were obtained from a hypertensive patient, they were selected because the same effect was demonstrated at all pressure levels and under differential spinal anesthesia. Similar records have been obtained from over 200 individuals with normal cardiovascular systems and under various anesthetics and in many stages of anesthesia. Premature contractions and dropped beats in otherwise normal rhythms are perhaps the simplest events producing prolonged diastole independent of reflex and humoral effects. Undoubtedly under these conditions the cardiac response in man conforms to Starling's law.

II. *Reflex Effects Which Modify the Strength of Myocardial Contraction.*

A. *Carotid Sinus Reflexes.* Figures 2 and 3 show the effects following prolonged diastole by carotid sinus stimulation. It is to be noted that the prolonged filling time is not followed by a more forceful contraction under these conditions. In all cases in man where we have been able to produce bradycardia by stimulating the carotid sinus, the period of prolonged diastole is followed by a less forceful contraction as evidenced by a smaller pulse pressure and altered contour. This effect is independent of the type of conduction; it occurs in complete heart block as well as in simple prolongation of the P-R interval.

It seems most likely that this unexpected response was due to a primary weakening of the ventricular myocardium so that it did not respond to an increased filling with an increased output. Other alternatives have been considered: (1) A stronger contraction might have taken place with its effect on the pres-

sure pulse masked by concurrent changes in arterial distensibility; experience with pulse wave velocity measurements[5] and examinations of the records indicates, however, that this is apparently not effective in that degree. Also the pulse contour and the pressures at the end of prolonged diastole indicate that marked peripheral vasodilatation did not mask the effect of a stronger contraction. (2) A simultaneous decrease in cardiac filling might have prevented a beat of increased strength following the prolonged diastole in many of these instances. But during carotid sinus stimulation the neck veins became evident as a result of distention; also, with periods of diastole lasting 15 to 18 seconds, cardiac fill-

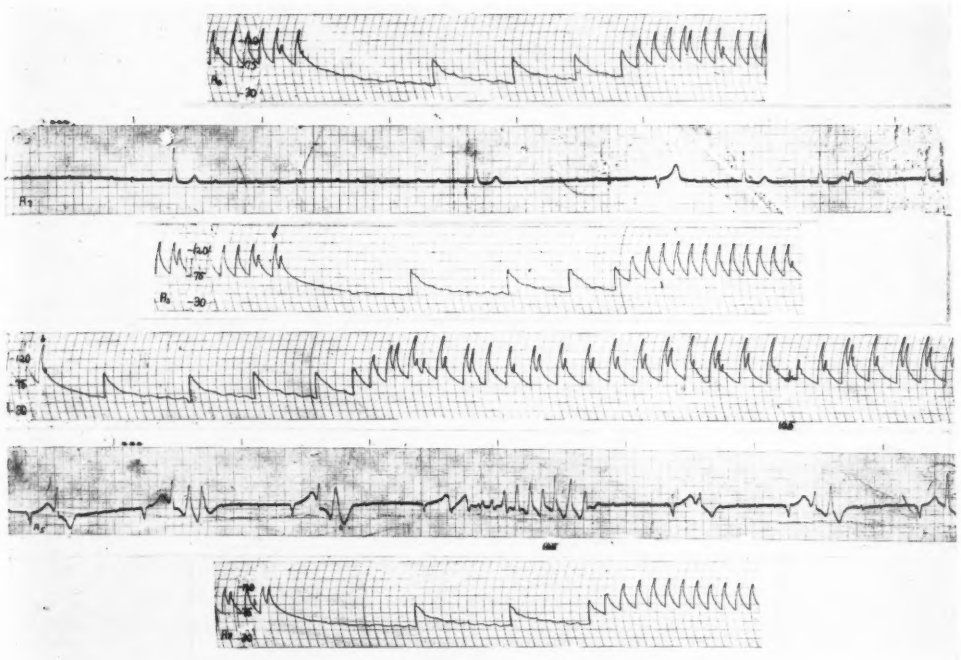

FIG. 2. Effects following stimulation of the carotid sinus. Intra-arterial and electrocardiographic records were obtained during an operation designed to denervate the left carotid sinus in a patient with complete heart block who had suffered a number of Stokes-Adams attacks following pressure on the sinus area. At operation no tumor could be found in the area and microscopic examination of tissue showed no structural abnormality. Extensive examinations including ballistocardiograms failed to uncover any co-existing disease or abnormality of the myocardium.

Upper record demonstrates the prolonged periods of asystole which followed stimulation of the carotid sinus. All such periods in this patient followed an extra systole. The vertical lines represent 1 second. The next lower record is Lead III of the simultaneous electrocardiogram (heavy vertical lines represent 0.20 sec.). Note that during the asystole the P waves continue at their regular rate. The third and fourth sections (time marked as in strip 1) demonstrate that asystole follows stimulation within one to two seconds. The number 105 seen in the fourth record identifies a run of a form of ventricular tachycardia which is also seen in the lower electrocardiographic record. Note that during this period of tachycardia the mean blood pressure does not continue to fall; however a Riva-Rocci determination would not give a blood pressure since the pulses are too small to give an audible sound. Atropine (1.2 mg.) was given intravenously one minute before the lower record was obtained. While the effect of atropine is somewhat equivocal, it may be seen that the pulses following prolonged diastole are not as markedly weakened as are those in the records obtained previously.

ing would have to cease almost completely in order to prevent some increased cardiac distention. In addition, observations upon both man and animals have shown that the reduction in pulse and mean pressure which follows decreased cardiac filling, as by constriction of the vena cava, comes on gradually during a number of beats. (3) That the overdistention of the heart could cause the weakened response also seems unlikely. In the Valsalva experiment cardiac filling is almost certainly augmented, but an equivalent, prolonged di-

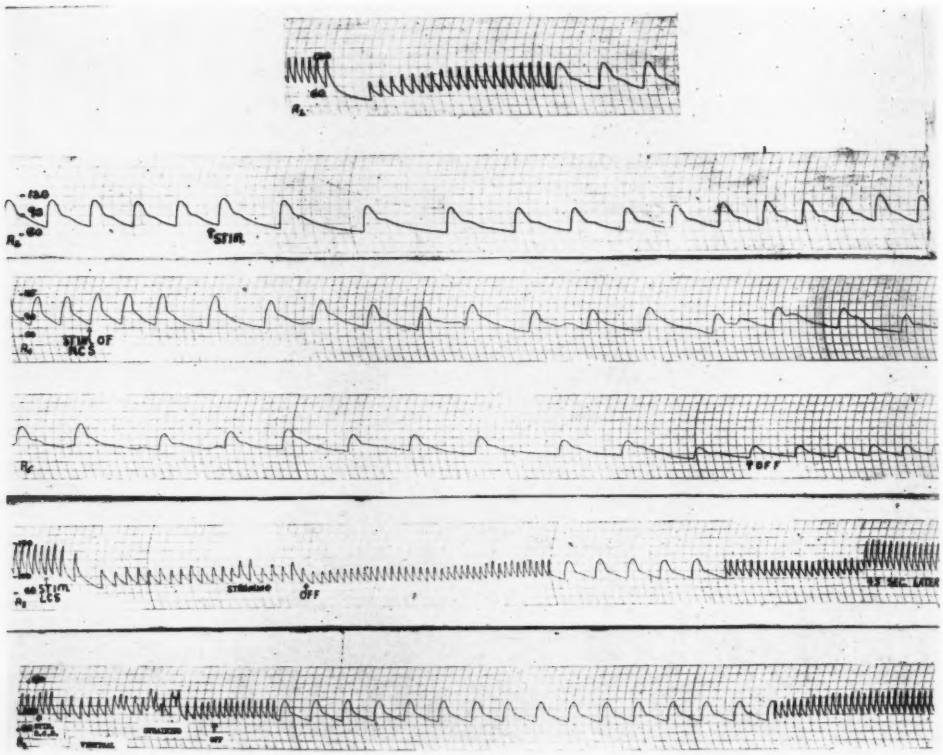

FIG. 3. Effects following stimulation of the carotid sinus. The upper record was obtained from a 37 year old man who had suffered no symptoms suggesting a hypersensitive carotid sinus; yet stimulation of the right sinus produced a period of prolonged diastole which was followed by a weakened contraction. Vertical lines represent 1 second except for the last three pulses during which time the lines are 0.20 second apart. Stimulation of the left sinus area was without effect.

The second, third and fourth sections were obtained during an operation designed to denervate the right carotid sinus in a 30 year old patient who had suffered syncopal attacks which would be reproduced by digital pressure over the area. The vertical lines in these records are 0.20 second apart.

The lower two records were obtained from a hypertensive patient who had not suffered syncopal attacks suggesting a hypersensitive carotid sinus. Note that the blood pressure and pulse pressure is depressed for a longer period than the pulse rate following stimulation. Note also that straining during the period of stimulation causes increases in the mean and pulse pressure. Subjects frequently respond to the rather uncomfortable digital pressure on their necks by straining. If Riva-Rocci determinations were made during these periods of strain the background hypotension would not be manifested. The vertical lines, again, are 1 second apart except for obvious periods when the paper was speeded to 5 times the original speed. Electrocardiograms were also obtained during these procedures; however they showed only a prolonged P-R and P-P interval.

astole is regularly accompanied by an increased pulse pressure. In addition the weak response occurs in some cases with relatively shorter periods of bradycardia following carotid sinus stimulation than is seen following extra systoles.

The want of a satisfactory alternative has led to the belief that carotid sinus stimulation causes not only an inhibition of the pacemaker but also a weakening effect upon the ventricles themselves. This is contrary to the usual teachings in regard to the effects and mechanism of the carotid sinus reflex, for the classic concept holds that the only cardiac effects are those which follow the inhibition of the pacemaker and that the vagus itself does not affect the ventricles directly. The available evidence has indicated that the response to carotid sinus stimulation is mainly mediated through the vagi and that sympathetic inhibition contributes only a small influence and then only after a latency of ten to fifteen seconds.[6]

It is commonly stated that stimulation of the carotid sinus or of the vagi directly produces bradycardia effects which are in accord with Starling's law. Bazett[7] states that following vagal stimulation, "the force of ventricular contraction is normally much increased owing to a greater filling resulting from a longer diastole." This view, common to all texts of circulatory physiology read by this author, is based upon many observations of the augmented pulse pressures which occurs during vagal or carotid sinus stimulation in animal experiments. Recently Ring, Michie and Oppenheimer[8] observed changes in the ballistocardiogram, electrokymogram and pulse pressure records following vagal stimulation of intact dogs. They found that in anesthetized dogs the period of prolonged filling was followed by a more forceful beat and thus concluded that the heart dilated and ejected more blood in accordance with Starling's law.

Indeed Drury[9] attempted to eliminate the complication of bradycardia during experiments designed to determine whether the vagus nerves had any direct action on the strength of contraction or refractory period of the ventricles. He prevented the slowing by driving the ventricles electrically during the period of vagal stimulation. In spite of the difficulty in interpreting Cushny myograph records and the abnormal concurrent stimulation of the ventricles, Drury concluded that the vagi had no effects upon the ventricles. It should be remembered that the vagus nerve trunk is composed of many afferent and efferent fibers and that certain fibers have different properties than others, hence data based upon stimulation of the total nerve trunks may be misleading. A recent publication[10] contained evidence that three entirely different responses followed carotid sinus stimulation in different species of animals and with different anesthetic agents. Many previous experiments were performed with slow mercury manometers or with manometers sufficiently underdamped to produce overshooting of the pulse recording. There seems to be no indisputable evidence denying the possibility that certain fibers which course the vagi directly affect the ventricles and previously reported data of the type illustrated here, especially from man, is quite meager.

B. *Reflexes from the Viscera.* Another unexpected reflex response was seen following traction on the visceral mesentery (fig. 4). During traction on the colon there appeared an abrupt fall in systolic and pulse pressure which disappeared promptly on release. This effect could be repeated at will and it persisted for as long as 20 seconds, which was as long as the traction was maintained. The same blood pressure effects have also been seen following gall bladder distention. It is noteworthy that there was no change in the pulse rate during this period of apparent weakening of myocardial contraction.

Because of its rapidity of onset and disappearance this effect can hardly be due to reduced filling. Nor will a reduction of peripheral resistance explain it, for the slight reduction of diastolic pressure was accompanied by a far greater reduction of systolic pressure and this, together with a consideration of the contour of the pulse, indicates that diminution of peripheral resistance is absent or slight.

What was probably a similar reflex effect on the heart was noted by Starr,[11] who observed a reduction in the magnitude of the ballistocardiogram complexes following distention of

the bile ducts by injecting fluids through a T-tube placed in the common duct at operation.

Comment. Thus several reflex responses have been demonstrated which depress the strength of cardiac contraction; in one case this is associated with a slowing of the pulse, while in the other it is mediated by a mechanism which has no influence upon the pacemaker. The results raise several fundamental questions. If vagal activity is solely responsible for the weakening effect, why is there not a bradycardia following mesenteric receptor stimulation as there is during carotid sinus stimulation? If the cardiac depression is induced by sympathetic inhibition why do these effects appear and disappear so rapidly? We are apparently dealing with a direct effect on ventricular muscles such as would occur if the responsible fibers entered the ventricles directly.

No classic concept will explain these phenomena. The results of the classic physiologic experiment in animals have been interpreted to mean that parasympathetic fibers have no direct effects upon the ventricle. Also, the response to changes of sympathetic activity occurs after a latent period, and the response persists for a time after such activity has ceased. But, as will be pointed out again, the evidence supporting the belief that vagal fibers do not penetrate the ventricles is not infallible, and, if sympathetic inhibition plays a role in the phenomenon we observe in man, such inhibition must occur far more rapidly and quantitatively in man than seems likely from the results secured in animals.

III. *The Relationship of Pulse Rate to Other Cardiovascular Alterations.*

Under this heading will be presented other data secured on man which seems inconsistent with the classic physiologic concepts. Marey's law states that the pulse rate is inversely proportional to arterial blood pressure. The common relationship found in animals, alterations of heart rate caused by changes in venous return and venous pressure, are attributed to the McDowell and Bainbridge reflexes. The following examples of the results secured in man are offered as evidence that none of these generalizations can be used to predict the pulse rate response in many situations found in the clinic. In addition to the well known pressure receptors in the great veins, pulmonary vasculature, carotid sinuses and aortic arch, there are receptors in the more distal part of the body which may exercise a dominating control over the pacemaker.

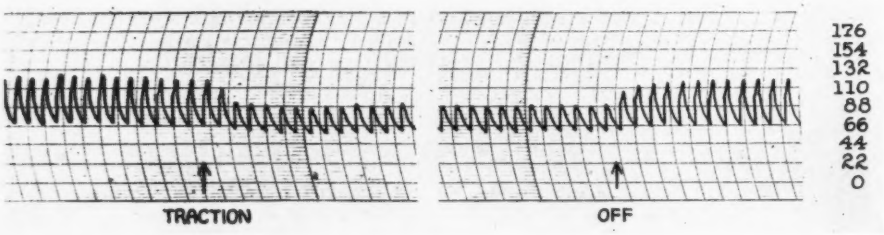

FIG. 4. Effect of traction or distension of the mesentery. Such traction produced an immediate drop in pulse pressure. Release of traction resulted in an immediate return to normal. No such effect occurred following traction on the colon after removal of the mesentery. This effect was not the result of any mechanical effect upon the large vessels in the abdominal cavity. This effect could be repeated at will.

Results Obtained during Spinal Anesthesia. Figure 5 represents a response which was predictable on the basis of existing generalities. Following the administration of amyl nitrite the pulse pressure fell, the dicrotic notch disappeared and the pulse rate rose rapidly. A considerable amount of blood was pooled in the legs. The legs were then elevated; the blood pressure rose as the stroke volume increased and the pulse rate accordingly slowed. All this would be expected from our knowl-

dge of classic physiology. Blood which accumulated in the legs because of vasodilatation, increased the venous return when the legs were elevated.

pressure fell and his pulse rate increased. After a differential spinal anesthesia this procedure was repeated and then while his blood pressure fell as it had before, his pulse rate fell markedly.

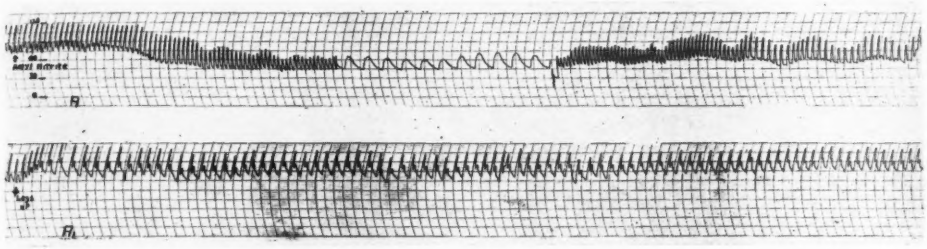

FIG. 5. Typical effects following administration of amyl nitrite in the supine position. Section A: At arrow amyl nitrite was inhaled. Note that the dicrotic notch drops out and the blood pressure begins to fall. Except for the period of eleven beats seen in the middle of this section the vertical segments indicate 1 second. Note the marked increase in respiratory variations of blood pressure. Section A_1: At arrow the legs was elevated. Note the abrupt rise in pulse and mean blood pressure and the resulting slowing of the pulse rate.

Figure 6, on the other hand, demonstrate an entirely different response. In this case, during spinal anesthesia there were changes of arterial blood pressure which were quite similar to those following administration of amyl nitrite to the previous case; but, in the presence of spinal anesthesia, there was no acceleration of the heart. The patient reported absence of sensations below T-12 and the flushing and warmth of the lower limbs, measured by skin temperature, indicated pooling of blood in the extremities. Elevation of the legs produced an increase in stroke volume and blood pressure but again there was no change in heart rate. With anesthesia only to a level of T-12 we must presume that the nervous pathways from the aortic arch, carotid sinus and great veins were left intact. Nevertheless the usual pulse response was blocked. Evidently there are receptors and pathways mediated, in part at least, through the lower segments of the spinal cord which play an active role in the regulation of the heart's rate. In a previous publication[1] a response was illustrated, but not described in detail, which demonstrates the complexity of these reflex pathways. A patient, who had had a sympathectomy from T-6 to L-3 for hypertension, was tilted to 70 degrees, the head being up, whereupon his blood

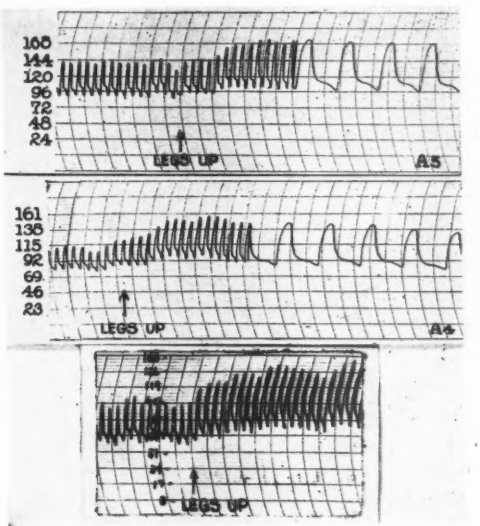

FIG. 6. These records demonstrate that, following spinal anesthesia to a sensory level of T-12, raising the legs above the level of the body while the patient is in the supine position causes a marked increase in pulse and blood pressure but no slowing of the pulse. The prolonged beats seen at the right of the upper 2 records result from speeding the recording paper. Except for these sections the vertical segments are 1 second apart. The hypotension following spinal anesthesia is, likewise, not followed by an acceleration of the pulse rate. Such a response has been noted following spinal anesthesia to a sensory level of T-10.

This observation has since been repeated in each of 6 patients tested.

To recapitulate: in the first case, after amyl nitrite the blood pressure fell and pulse rate rose. In the second, after a similar fall of blood pressure, pulse rate was unchanged. In the third, after a similar fall of blood pressure, pulse rate diminished. There was also a dissimilar response to an increase in blood pressure brought about by raising the legs. In these 3 cases the reflexes from the carotid sinus, aortic arch and great veins must be thought of as being intact. The difference of response must be attributed to differences in

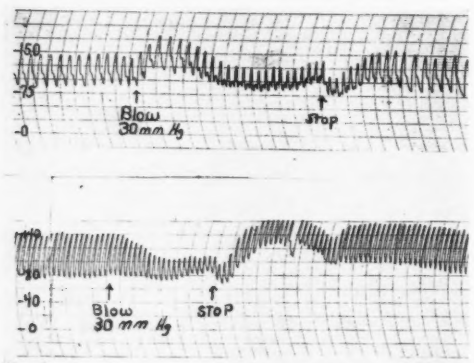

FIG. 7. Upper Record: Intra-arterial pressures obtained from a normal young man during the Valsalva experiment. At the arrow marked "blow 30 mm. Hg" the subject blew against a mercury column. At the arrow marked "Stop" this effort was relaxed. Lower Record: Records obtained by the same procedure in a hyperthyroid patient.

reflex mechanisms in the lower part of the body which thus seem either to facilitate normally or, under these conditions, to prevent the response associated with the receptors mentioned above.

Normally, tilting the head up results in well known changes. The pulse accelerates as the upright position is approached and when the proper correction for gravity is made it is found that the mean blood pressure at the level of the carotid sinus falls, that the pressure at the level of the aortic arch usually is unchanged and that the pressure below the aortic arch rises.[12]

Results Secured during the Valsalva Maneuver. In a large series of subjects who performed the Valsalva maneuver it was found that there were individual variations in the degree of pulse rate and blood pressure responses; however, all normal unanesthetized subjects showed acceleration and deceleration of the pulse rate with decreases and increases in blood pressure. Figure 7 demonstrates this typical response and, in contrast, the response seen in each of 2 hyperthyroid patients tested. In the latter the pulse rate is completely uninfluenced by marked changes in blood pressure, which were doubtless accompanied by equally marked changes in venous return, cardiac output and peripheral resistance.

This difference in response in hyperthyroidism is perhaps comparable to results secured on animals. Rein[13] stated that when vasodila-

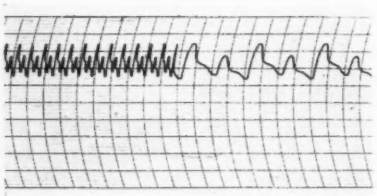

FIG. 8. Intra-arterial recording which is typical of the pulsus alternans seen so often following cyclopropane anesthesia.

tation occurs in an organ as the result of increased work or demand, it does not respond normally to humoral or nervous influences. Hamilton[14] has noted the same failure of rate changes in dogs with aortic insufficiency. These two conditions have, however, only the chronically widened pulse pressure, reduced peripheral resistance and rapid pulse rate in common with hyperthyroidism.

Arrhythmias Noted during Surgery. During surgery within the thorax we, as well as others, have noted a large variety of cardiac arrhythmias of reflex origin due to manipulation of the lungs and pulmonary vasculature. Figure 8 demonstrates the pulsus alternans seen so frequently during anesthesia produced by cyclopropane. Stutzman[15] has shown that this reflex is mediated through the coeliac plexus. Anesthetists know that ether, when added to the anesthesia mixture, will usually abruptly

stop this arrhythmia. During an operation of carotid sinus denervation there appeared a marked increase in extra systoles and tachycardia as shown figure 2. in Following the infiltration of the adventitia of the carotid vessels with procaine this irritability disappeared.

IV. *Results Indicating a Direct Vagal Influence upon the Ventricles.*

Data already presented in this communication have suggested that certain nerve fibers influence the ventricles directly without affecting the pacemaker. Certainly the effects recorded in these patients were not consistent with presently accepted characteristics of sympathetic activity. Therefore our data is in conflict with the generally accepted belief that the vagal branches do not innervate the ventricles and that the only parasympathetic action upon the ventricles is a result of an effect upon the sinus or A-V node. It is commonly taught that ectopic ventricular rhythms cannot be inhibited by reflex vagal stimulation, as can sinus or nodal arrhythmias, and Robb[16] knows of no anatomic evidence clearly demonstrating or refuting vagal-ventricular innervation in man. There are, however, species variations and such anatomic evidence is quite difficult to obtain.

However, data are shown in this paper which support the view that certain vagal fibers do effect the ventricles directly. One of the subjects had a complete heart block in addition to, or as a result of, a hypersensitive carotid sinus. There was no history or clinical evidence of heart disease in a morphologic sense. The heart was not abnormally enlarged and there was no history of congestive failure. It can be seen from figure 2 that there was complete dissociation of the ventricles from the auricles and the electrocardiogram indicates that the focus of the ectopic rhythm were located below the A-V node.

Stimulation of the carotid sinus by pressure caused asystole of the ventricles yet, at the same time, auricular activity persisted at almost the previous rate.

This may be an unusual phenomenon, but there have been numerous reports in the literature[17–22] concerned with an acceleration of the pulse rate following atropine administration during complete heart block; two of these are worthy of additional comment. Salley[21] reported one "unusual" atropine effect on ventricular tachycardia following coronary thrombosis. Following administration of atropine the ventricular rate dropped to 30 thus uncovering a complete heart block. In view of Drury's[9] previous report, Salley concluded that atropine may have had a direct action upon the ventricles. Field, Barker and Alexander[22] reported a case in which direct faradic stimulation of both vagi failed to influence the heart in any degree. A few days later, however, similar stimulation produced a slowing of the ventricular tachycardia. Messer and co-workers[23] have mentioned some of the problems in interpreting data based upon the use of drugs. In the case represented in figure 2, following the intravenous administration of 1.2 mg. of atropine, a marked prolongation in the diastolic period was not followed by the same degree of weakening as previously, yet the heart rate was not changed significantly.

A consideration of the data reported here and by others suggests that such results have been found frequently and that the only unusual feature is that they do not conform to expectations based upon the results obtained by Drury and others working on more or less isolated systems and upon anesthetized animals. In view of the results obtained on man, it seems unjustifiable to exclude the possibility of direct parasympathetic effects on the ventricles in man. This innervation may, however, vary functionally or anatomically from one person to another.

V. *The Peripheral Aspect of Reflex Activity.*

Weiss and Baker[24] secured data obtained by Riva-Rocci measurements to indicate that, following carotid sinus stimulation, blood pressure returns to normal more rapidly than the pulse rate. This they interpreted as indicating that the slowing of the pulse is but one manifestation of this reflex and that it is less important than vasodilatation in controlling blood pressure.

The data presented here do not confirm this

hypothesis entirely. Except for one individual who had hypertension (see fig. 3), it can be seen that after the cessation of carotid sinus stimulation the return of the blood pressure to normal is accompanied by increased pulse pressure and so is mainly a consequence of cardiac action. The difference of response in the patient with hypertension may have been due to a depression of cardiac strength which persisted beyond the depression of cardiac rate. The slope of the pulse contours and the fact that the pressure during asystole levels off well above colloid osmotic pressure are effects not consistent with marked vasodilatation.

It can be seen from the pressure levels and pulse contours shown in figure 4 that stimulation of mesenteric receptors in man resulted in little if any peripheral vasodilatation, for the systolic pressure dropped markedly while diastolic pressure dropped only a small amount, so it is the change in systolic pressure which is chiefly accountable for the fall in mean pressure. Gammon and Bronk,[25] in describing the activity of the pacinian corpuscles in the mesentery, and Heymans and co-workers,[26] who also worked on this reflex, disagreed about the peripheral vascular effects following stimulation of these receptors. In their publications they did not concern themselves with cardiac effects. The difference in result may be due to the different species of animals and different anesthetic agents used by the 2 groups.

VII. *General Considerations of Reflex Activity.*

When one attempts to consider the significance of such observations as these and to cover the literature which exists concerning cardiovascular reflexes, it is impossible not to ask the same question that Heymans asked[26]: "Are all vessels provided with reflex propriosensitivity?"

The evidence is increasing that reflex effects on the heart can arise from many locations in the body. In addition to the well known carotid sinus, aortic arch and mesenteric receptors, reflex activity has been associated with the great veins, the right auricle, the pulmonary vasculature, the ventricles, and yet the list is by no means complete. Angina-like symptoms have been associated with biliary disease[27]; carotid sinus stimulation has produced[28, 29] as well as relieved [30, 31] such a pain. Vascular changes have been correlated with activity of the stomach.[32]

Hitherto, the expectations of clinicians have been largely based on physiologic data secured in experiments on anesthetized animals. Evidence has now been presented to show that, when certain of these reflexes are stimulated or modified by anesthesia, there are marked differences in the manner in which the cardiovascular system readjusts to changes within itself. Similar modification of reflex response doubtless occurs in conditions of disease, and certainly many manifestations of disease are unexplained by existing morphologic changes in the cardiovascular system. While one may doubt whether reflex imbalance can be considered the sole cause of any single cardiovascular derangement, an understanding of the physiologic changes found in disease requires a knowledge of the many reflex mechanisms concerned with cardiovascular adjustments. Abnormality of the adjustments may amplify, out of proportion, the effects of morphologic lesions themselves. Observers in the past have suggested that during rheumatic fever there is an alteration of vagal tone.[33, 34] Stead,[35] Richards[36] and others have repeatedly emphasized the complexity of attempting to relate cardiac filling pressure and cardiac output. The inability to relate these factors with any consistency is encountered not only in disease but in many physiologic events. Undoubtedly reflex changes such as those demonstrated in this paper are concerned with the ability of the heart and circulation to adjust to the needs of the moment, and they must be thought of as playing an important part in the symptomology and pathogenesis of the many abnormalities of function so often found in disease of the heart and circulation.

Summary

1. Data including selected records of direct intra-arterial blood pressures and electrocardiograms secured from almost 1000 subjects are shown. These records have been obtained from

man during anesthesia, surgery, clinical disease, physiologic and pharmacologic experiments.

2. The records chosen for presentation were selected because they demonstrate the occurrence in man of cardiovascular reflex responses that are not generally recognized and are not explainable by existing concepts of reflex effect.

3. The stimulation or alteration of certain reflex areas has been seen to produce an apparent primary weakening of ventricular contraction (in some cases concurrent with the induction of bradycardia, and in others independent of changes in the pacemaker system of the heart) in addition to indicated alterations in stroke volume, cardiac filling and arterial pressure.

These changes follow modifications of reflex systems which are said to mediate their activity upon the heart through the vagus nerves. In addition the effects are not consistent with the presently accepted response of the sympathetic nervous system. These reflexes modify the manifestation of Starling's law, but to say that Starling's law does not hold in man is to deny the existence of reflex and humoral cardiovascular effects.

4. Spinal anesthesia to a sensory level of T-12 has abolished the classic response of the pulse rate following changes in stroke volume, cardiac filling and arterial pressure.

5. From the type of evidence listed in 3 and 4 it has been concluded that either there are certain fibers from the vagus nerves which enter the ventricles directly and produce an effect of weakened strength of contraction or that sympathetic inhibition occurs far more rapidly and quantitatively in man than has been supposed previously.

6. Some general considerations of the significance of alterations of reflex balance in man are attempted.

Acknowledgments

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The Isolation of Hypertensin from the Circulating Blood of Dogs by Dialysis in an Artificial Kidney

By JOSEPH R. KAHN, M.D., LEONARD T. SKEGGS, PH.D., AND NORMAN P. SHUMWAY, M.D.

A vasopressor substance has been dialyzed out of the circulating blood of dogs by means of an artificial kidney. This substance is similar to hypertensin. It has been recovered from normotensive and hypotensive dogs and from animals with malignant hypertension. The method for concentration of this substance in the dialyzate is described and concentration data which, due to the loss in recovery, is only roughly quantitative, is given.

THE PRESENT VIEW of the mode of development of experimental renal hypertension[1] is that a chemical mechanism causes the elevation of the blood pressure. The components of this mechanism are the renal enzyme, renin, its plasma substrate, hypertensinogen, and the vasopressor substance, hypertensin, resulting from the interaction of renin and hypertensinogen. It is of paramount importance for the acceptance of the renin-hypertensin theory that the vasopressor substance, hypertensin, be present in the circulating blood and be recoverable from it in suffient amounts to account for the elevation of blood pressure in animals with experimental renal hypertension. The presence of renin in the circulating blood has been demonstrated by indirect means[2] but the existence of hypertensin in the circulating renal venous or systemic blood of man and experimental animals has not been demonstrated beyond question. It has been presumed that the failure to recover hypertensin was due to its destruction by the enzyme, hypertensinase, or the immediate removal of hypertensin from the blood by its combination with smooth muscle in the walls of the arterioles. The other possibility is that hypertensin is an artefact, formed only in vitro by the action of renin on hypertensinogen. Hypertensin is a polypeptide of low molecular weight, about 2700,[3] and slowly dialyzable through a cellophane membrane. We found that it took one to two hours, in aqueous solution, to reach equilibrium across the membrane in the artificial kidney. It occurred to us that, if hypertensin be present in the circulating blood of normal or hypertensive animals, it might be separated from it by subjecting the blood to dialysis in a suitable artificial kidney. For this purpose, we used the artificial kidney described by one of us.[4]

From the Department of Medicine and Surgery, Veterans Administration Hospital, and the Institute of Pathology and Department of Medicine, Western Reserve University, Cleveland, Ohio.

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EXPERIMENTS

Dogs were used in all of the experiments. They received morphine sulfate, 7.5 to 15 mg., and atropine sulfate, 0.5 mg., before the beginning of the experiment. The artificial kidney was connected to the femoral artery and femoral vein by means of rubber tubing.

The pressure in the femoral artery produces a rapid flow of blood through the kidney making it unnecessary to introduce a mechanical pump into the blood side of the system.

The circulating blood of the animals was dialyzed for three or four ninety-minute periods against 500 ml. of circulating dialyzate. The composition of the dialyzing solution was Na^+ 148, Ca^{++} 5, K^+ 3, Mg^{++} 3, Cl^- 126, HCO_3^- 24, HPO_4^{--} 2, and lactate$^-$ 7 mEq./liter plus 100 mg. of glucose/100 ml. The pH of the solution was 7.35 to 7.45. At the end of each period the dialyzate was collected, measured and placed in round bottom flasks in which it was frozen by rotation of the flasks in a

mixture of dry ice and acetone. All of the dogs were heparinized. At the beginning of the experiment, they were given 4 mg./Kg. of heparin, intravenously, and throughout the experiment, they were given 0.5 mg./Kg./hour. The blood flow through the kidney was regulated by a screw clamp on the rubber tubing which returned the blood from the kidney to the femoral vein. Only in the hypertensive dogs was the blood flow of such magnitude that it had to be reduced by constriction of the lumen of the rubber tubing. The blood flow through the kidney ranged between 100 to 200 ml./minute. Four units of the kidney were used. The dialyzing surface was 6,800 sq. cm., and the capacity was 200 ml. of blood and 200 ml. of dialyzate. Number 300 mm. moisture proof Dupont cellophane was used as the dialyzing membrane.

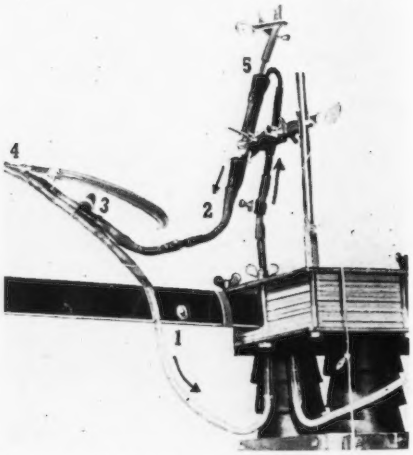

FIG. 1. Artificial kidney and tubing connecting it to the dog. The arrows indicate the direction of the blood flow. (1) Tubing connecting the femoral artery with the kidney, (2) tubing returning the blood from the kidney to the femoral vein, (3) thermometer inserted into the venous return, (4) needle inserted into the arterial tubing for recording the blood pressure, (5) air trap.

There was a marked fall in the blood pressure of two of the animals after they had been attached to the artificial kidney for ten minutes. The blood pressure gradually rose again until it reached normal in one or two hours. It has been found that the fall in blood pressure was due to a toxic material which was present in the cellophane and which could be removed by boiling the cellophane in distilled water for twenty-four hours. Subsequent to this procedure no further hypotensive periods were observed in the dogs.[5] Hypertensin was recovered from the dialyzates of these two animals which sustained a fall of blood pressure. Of what importance the recovery of hypertensin is in these two animals cannot be stated, since hypertensin was also present in the dialyzates of three normal animals in which there was no appreciable fall of blood pressure.

After the kidney was assembled, it was sterilized by passing steam through both the blood and dialyzate sides of the apparatus for thirty minutes and then was washed with five liters of sterile pyrogen-free saline.

The dialyzate, that is the solution against which the blood was dialyzed, was pumped through the kidney by means of an electrically driven rotary pump at a rate of 200 cc./minute and at a negative pressure of 10 mm./Hg. The dialyzate flowed through a copper coil placed in a water bath which was maintained at 39 C. This maintained the temperature of the blood circulating through the kidney at 38.5 C. A thermometer in a T tube was inserted into the rubber tubing connecting the kidney with the femoral vein. In this manner, changes in the temperature of the blood could be regulated and noted throughout the experiment. A needle attached to a mercury manometer was inserted into the rubber tubing connecting the femoral artery with the kidney, so that the approximate mean blood pressure of the animal could be observed throughout the experiment. (See figs. 1 and 2.)

Before the experiment was started, 400 ml. of blood was collected by arterial puncture from a donor dog into a flask containing 40 mg. of heparin and 20 cc. of normal saline. This blood was used to fill the artificial kidney and the rubber tubing connecting it to the animal. The remaining 200 ml. of blood was given by a slow intravenous drip throughout the early period of the dialysis. The pressure of the blood in the kidney was then raised by addition of blood to it with a syringe until

it was equal to the arterial pressure of the dog whose blood was being dialyzed. By this procedure, there was no loss of blood or fall of blood pressure when the dialysis was started.

Normal donor dogs were used in three experiments. This procedure had to be abandoned because of the possible presence of renin or hypertensin in the blood of these animals. As a matter of fact, hypertensin was demonstrated in the dialyzate of all three of the animals which received blood from normal donor dogs. In order to be certain that the hypertensin, which was recovered in the dialyzate, came from the animals subjected to dialysis, bilaterally nephrectomized donor dogs were used. The animals were nephrectomized from 18–36 hours before they were bled.

All of the animals lost water during dialysis. The average loss was 100 ml. during the first ninety-minute period and 40–60 ml. during each subsequent one. Animals with hypertension may lose as much as 200 ml. of water during each period of dialysis. There is a filtration pressure across the cellophane membrane of 180 mm./Hg in an animal with a mean blood pressure of 170 mm./Hg; the artificial kidney, therefore, acts by ultrafiltration as well as by dialysis. In order to avoid dehydration, the animals must be given a constant intravenous infusion of dialyzate equal to the volume of water lost during each period of attachment to the artificial kidney.

At the conclusion of each experiment 150 mg. of protamine in 100 ml. of saline was administered intravenously to the animals to bring the clotting time back to normal.

Preparation of the Dialyzate

The dialyzates from the individual dialyzing periods, each approximately 600 ml., are shell frozen immediately in three-liter round bottom flasks in a dry ice-acetone bath. These are lyophilized, tightly stoppered and stored in the cold until further processing is possible. The dialyzate from each period is worked up as an individual preparation.

The dialyzate is reconstituted in concentrated form in the original flask by the addition to the dried cake of 5 ml. of 0.5 normal hydrochloric acid for each 100 ml. of original dialyzate. The flask is rotated until solution is complete, and the carbon dioxide gas is eliminated. The pH is adjusted to approximately 6.0, using small amounts of 2.5 normal sodium hydroxide and bromthymol blue as an external indicator. A thick yellow syrup is obtained at this stage, and it usually contains 80–85 mEq. of sodium. Nine volumes of anhydrous ethyl alcohol,

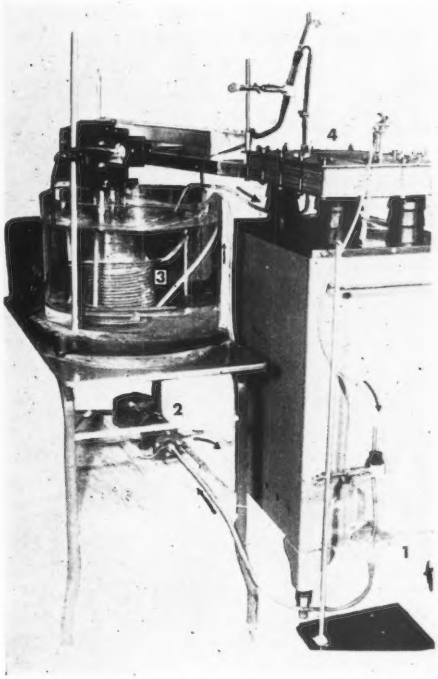

FIG. 2. Illustrates the circulation of the dialyzate through the kidney. The arrows indicate the direction of the flow of the dialyzate. (1) Reservoir for dialyzate (2) electrically driven rotary pump, (3) copper coil immersed in constant temperature water bath, (4) artificial kidney.

U.S.P., are added, shaken well, allowed to stand for thirty minutes and then the mixture is filtered and the precipitate is discarded. The alcoholic filtrate is evaporated under vacuum (at a temperature of less than 30 C.) to a volume 5–6 ml. This material contains between 20–30 mEq. of sodium. The pH is adjusted to 6.0±0.2 (glass electrode) and placed in a cellophane bag (Visking casing 2.8 cm. flat diameter) 12 cm. in length. This bag is rotated

on its axis at 120 rpm in a large horizontal glass cylinder partially stoppered and containing 10 ml. of distilled water. In this manner, these relatively small volumes of dialyzate are exposed to a constantly moving dialyzing membrane with an area of 65 sq. cm. Dialysis is continued for ten to twelve successive five-minute periods, the dialyzing water being removed and replaced with 10 cc. of distilled water at the end of each period until the total sodium within the cellophane bag is decreased to less than 0.15 mEq. The material is then removed from the bag and stored as fraction I. The dialyzing water is combined and evaporated under vacuum (at less than 30 C.) to a volume of 5–6 ml., placed in the same cellophane bag and subjected to the same dialyzing procedure. The dialyzing water in this case is discarded, and the material remaining in the bag, fraction II, is combined with fraction I. (The loss of hypertensin during these dialyses is 50–60 per cent.) One-half volume of ethyl ether, C.P., is then added to the solution which is shaken thoroughly and centrifuged. The ether layer is discarded together with the insoluble material formed at the ether-water interface. The clear water layer is de-etherized and evaporated to a small volume under vacuum. The pH is adjusted to 7.3±0.2 using sodium hydroxide, and the final volume is adjusted, so that each ml. represents 250 ml. of the original dialyzate. The preparation is frozen until it is assayed. The final product is clear, yellow and has a sodium concentration between 100 and 200 mEq. per liter, a potassium concentration of 5 to 15 mEq. per liter. The overall recovery of hypertensin, as estimated by adding it to one of two identical aliquots of the original dialyzate, is between 10 and 30 per cent. Performing all of the procedures in the cold does not improve the yield of hypertensin nor do small changes in the pH values appreciably change it.

Assays of the dialyzates are performed on mature rats anesthetized with Nembutal, 5 mg. per 100 Gm. of body weight. Both vagus nerves are cut and the trachea is cannulated. A needle is inserted and tied into the left jugular vein; this is used for intravenous injections of the material to be assayed. The right carotid artery is cannulated and connected with a calibrated double rubber membrane manometer (Phipps and Bird) equipped with a pen for ink writing on a kymograph.

Rats are used in this experiment since 0.01 of a unit of hypertensin (Goldblatt)[6] produces an appreciable rise in blood pressure, the average rise in the arterial pressure from this dose is 25 mm./Hg. The average normal blood pressure of the anesthetized rat with the vagi sectioned is between 100 and 175 mm./Hg.

All of the tests on the dialyzates are done with small volumes ranging between 0.25 and 0.50 ml. The rises in the rats' blood pressure are compared with those obtained by the injection of 0.01 unit of hypertensin prepared from standardized lyophilized powder. One unit of this standard gave an average rise in blood pressure of 32 mm./Hg in 12 nembutalized rabbits and an average 30 mm. rise in seven unanesthetized dogs. This unit is approximately equal to the Goldblatt unit.

Eleven of the dialyzates which had pressor effect were tested for their susceptibility to destruction by one or several of the following substances: hypertensinase, trypsin, acid (pH 1.0 at 100 C. for ten minutes) and alkali (pH 12.0 at 100 C. for ten minutes).

The hypertensinase used in these experiments is prepared by hemolyzing one volume of freshly drawn rat blood by adding it to eight volumes of water. One volume of 10 per cent sodium chloride and one volume of 1:1000 solution of Merthiolate are then added. The pH of this solution is adjusted to 7.4±0.1, centrifuged and 0.5 volume of the clear supernatant fluid is added to a suitable aliquot of the active preparation. The mixture is incubated for two hours at 37.5 C. Following incubation, the solution is kept frozen until it is assayed.

A solution of trypsin is prepared by dissolving a small amount of Armour's crystalline trypsin in water. It is then dialyzed to eliminate $MgSO_4$ and a sufficient amount of 1:1000 solution of Merthiolate is added to give a final concentration of 1:5000. The pH of the solution is adjusted to 7.4. This solution of the enzyme is prepared so that it contains 1.03 to 1.50 mg. of nitrogen per ml. as determined by the

micro Kjeldahl method. One-fifth volume of this enzyme preparation is added to a suitable aliquot of the active dialyzate, and the mixture is incubated for two hours at 37.5 C. At the end of the period of incubation, the mixture is placed in a boiling water bath for ten minutes. After cooling and centrifuging, the clear supernatant fluid is withdrawn and frozen until it is ready to be assayed.

Several control tests are performed using heat inactivated trypsin and hypertensinase.

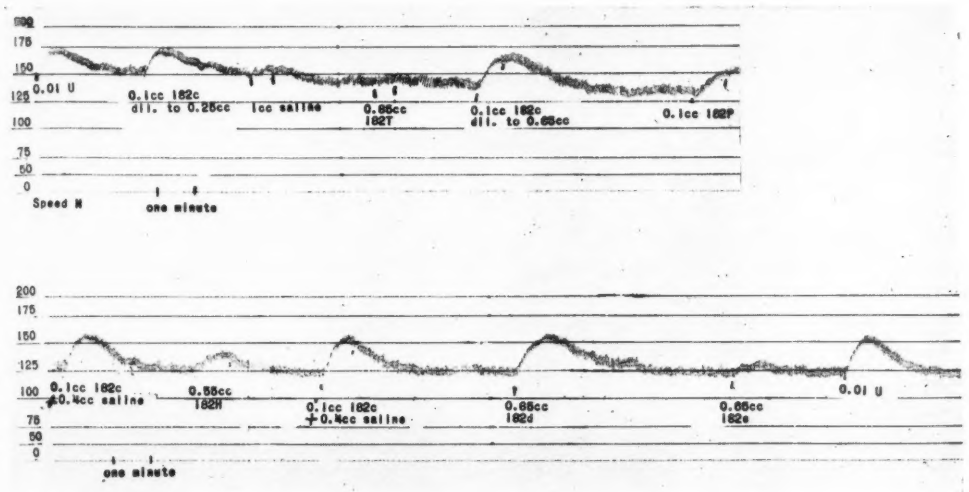

FIG. 3. Recording of mean blood pressure in the carotid artery of a rat. The first rise is produced by the injection of 0.01 unit of hypertensin. The second rise is produced by the injection of 0.1 ml. of dialyzate from Dog 13 (Churchill) with malignant hypertension. 0.1 cc. of this material represents 24 ml. of original dialyzate. 0.1 cc. amounts of this preparation were incubated with trypsin (182T), hypertensinase (182H), boiled at a pH of 1 (182d), and boiled at pH of 12 (182e).

The susceptibility of the pressor substance in the dialyzate to destruction by alkali or acid is tested by changing the pH of suitable aliquots to 1.0 or 12.0. These solutions are heated in boiling water for ten minutes, cooled, and the pH readjusted to 7.3±0.2.

RESULTS

Group I: In 9 normal dogs the circulating blood was subjected to dialysis for 3 or 4 ninety-minute periods. Blood from bilaterally nephrectomized donor dogs was used to fill the artificial kidney. Hypertensin was recovered in the dialyzates of only two animals. The amount of hypertensin recovered was 0.04 unit per liter of dialyzate from each animal. No hypertensin was detected in the dialyzate of the remaining 7 animals.

Group II: Two normal dogs were subjected to dialysis for three ninety-minute periods. Blood from normal donor dogs was used to fill the artificial kidney. Hypertensin was recovered in the dialyzate from both of these animals. The amount of hypertensin recovered was 0.05 and 0.12 unit per liter of dialyzate.

Group III: Two normal dogs in which there was a marked fall in blood pressure during the experiment were subjected to dialysis for three ninety-minute periods. Blood from bilaterally nephrectomized donor dogs was used to fill the kidney. Hypertensin was recovered from the dialyzates of both of the animals. The amounts of hypertensin were 0.05 and 0.4 unit per liter of dialyzate.

Group IV: Nine normal dogs were given multiple intravenous injections of widely varying amounts of renin and subjected to dialysis for ninety minutes. Hypertensin was recovered in the dialyzates of only three of these animals. The amount of hypertensin recovered was 0.1, 0.15, and 0.7 unit per liter of dialyzate.

Group V: Two bilaterally nephrectomized dogs were subjected to dialysis for three ninety-minute periods. Blood from bilaterally nephrectomized donor dogs was used to fill the artificial kidney. No hypertensin was recovered in the dialyzates from either of the animals.

Group VI: Four dogs with malignant hypertension, produced by the Goldblatt method,[1] were subjected to a dialysis for three ninety-minute periods. Blood from bilaterally nephrectomized donor dogs was used to fill the artificial kidney. Hypertensin was recovered in the dialyzate of all four animals. The amount of hypertensin recovered was 0.4, 0.07, 0.5, and 0.04 unit per liter of dialyzate.

Discussion

By the use of an artificial kidney, a pressor substance has been dialyzed out of the circulating blood of intact animals which conforms to the usual tests for hypertensin: intravenous injections of 0.25 to 0.50 ml. produces an immediate steep rise in blood pressure, the maximum rise occurs in one minute or less, and the return to normal in three minutes or less. Repeated injections of the same magnitude do not produce tachyphylaxis. The pressor effect of intravenous injections of the dialyzate was unaffected by previous injections of cocaine, atropine or 933F but was potentiated by a previous injection of tetraethylammonium chloride. By the methods that were used in the preparation of the dialyzate, the pressor material has been found to be water and alcohol soluble, ether insoluble, and slowly dialyzable. In the dialyzates in which there was a sufficient amount of the pressor material, this substance was found to be destroyed by trypsin, hypertensinase, boiling at pH 12 but not at pH 1 (fig. 3). Eleven such preparations were tested by one or more of the above methods. In all cases the pressor effect was destroyed.

Summary

A pressor substance has been dialyzed out of the blood of intact dogs by means of an artificial kidney. This substance conforms to all the usual tests described by Goldblatt and Edman for the identification of hypertensin.

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The Relationship between Prothrombin Time and Bleeding in the Clinical Use of Dicumarol after Operation

By C. Adrian M. Hogben, M.D., and Edgar V. Allen, M.D.

Experienced clinicians have known for some time that bleeding owing to the use of dicumarol is not entirely a measure of the degree of prothrombin deficiency. This presentation emphasizes that bleeding may occur when prothrombin deficiency is not great and that bleeding may fail to occur when prothrombin deficiency is marked. Nonetheless great prothrombin deficiency causes bleeding more frequently than lesser degrees of prothrombin deficiency. Time is an important factor, for patients are much more apt to bleed when prothrombin deficiency has endured for several days than when it has been present only a day or so.

SINCE the isolation and synthesis of dicumarol by Link and his co-workers,[1] its therapeutic value has been established.[2, 3] Bleeding is the only untoward effect of treatment with dicumarol. This report is an analysis of the relationship between prothrombin time and bleeding met in the clinical use of dicumarol.

The low incidence of bleeding (about 5 per cent of postoperative cases) which accompanies careful use of dicumarol has been associated with vigilant regulation of the dose of dicumarol dependent on daily determinations of prothrombin time. The method of determination of prothrombin times used at the Mayo Clinic is Magath's modification of Quick's procedure.[4] With this test, the respective values for 100, 30, 20 and 10 per cent of normal prothrombin activity are 17 to 19 seconds, 27 seconds, 35 seconds and 60 seconds. The therapeutic goal has been to reduce the prothrombin time to between 10 and 30 per cent of normal.

In our study, bleeding was considered to result from dicumarol in all cases. In some instances it would have occurred, obviously, had dicumarol not been used, as postoperative bleeding occurs occasionally when dicumarol has not been administered. It appears improbable to us, however, that the results of this study have been significantly influenced because we have considered all bleeding to result from dicumarol. We considered hemorrhage to have been minor (epistaxis, hematuria, ecchymosis and oozing from a surgical wound) if transfusion was not required and to have been major if transfusion was required.

In a group of 2456 cases, predominantly postoperative, in which the patients received dicumarol, there were 147 instances of bleeding. Records were maintained and every twentieth patient who did not bleed was used as a control. In the course of treatment, the mean prothrombin time rose rapidly at first and slowly declined to a fairly stable level (fig. 1). Because of this variation, we compared separately for each day of treatment and on the same day, the mean prothrombin time of patients who bled with the mean prothrombin time of controls. We considered the prothrombin time on the day of bleeding as the only significant figure for the bleeders, as the prothrombin time may have been low prior to bleeding, risen abruptly at the time of bleeding and declined subsequently owing to institution of countermeasures. Henceforth, when we speak of prothrombin time of the bleeders, we speak of the prothrombin time obtained only on the day of bleeding.

The mean prothrombin time of bleeders is higher in most instances than that of controls for the same day of treatment (fig. 1). In spite of the striking difference in mean prothrombin times, the relationship between bleeding and prothrombin is not a close one. Bleeding occurred in some instances when prothrombin time was not increased much above normal and failed to occur in other instances when prothrombin time was greatly increased (table

From the Division of Medicine, Mayo Clinic, Rochester, Minn.

1). The overlapping of prothrombin times of the two groups, controls and bleeders, is so great (fig. 2) that prothrombin time should not be used to predict the onset of bleeding or immunity from bleeding in the individual patient. Of all patients who had hemorrhages only 57 per cent had a prothrombin time greater than thirty-five seconds which was the desired value and one not generally considered to predispose to bleeding.

The mean prothrombin time of those who had major bleeding was higher than the mean prothrombin time of those who exhibited minor bleeding, but the same marked variations existed between bleeders, as a group, and controls (table 1).

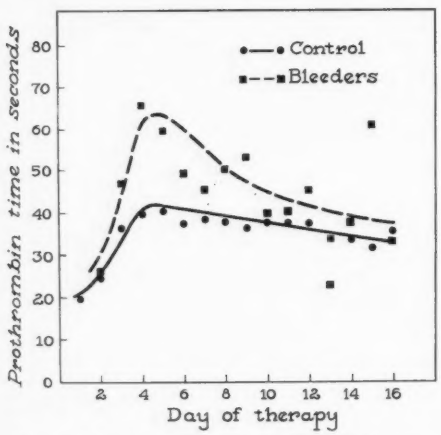

FIG. 1. Comparison of mean prothrombin times of control patients and those of bleeders by day of treatment. (Note: Values for bleeders are means of prothrombin times observed on the day of bleeding.)

Age was apparently not a factor in the incidence of bleeding. The mean ages of the different groups were: controls forty-nine years, minor bleeders forty-four years and major bleeders forty-seven years. The differences in incidence were not significant.

The daily incidence of bleeding is interesting. Hemorrhage induced by experimental administration of dicumarol to animals[5] and that which affects patients receiving excessive doses of dicumarol[6] may occur about two weeks after institution of treatment. In our series, the incidence of bleeding was greatest on the eighth day of treatment with a relatively high incidence from the sixth to tenth day. The infrequency of cases during the first few days might have been explained plausibly on the basis of delayed onset of prothrombin deficiency, but the mean prothrombin time reached a maximum by the fourth day (fig. 1) and slowly declined thereafter while the incidence of bleeding increased. We could not attach special significance to the lower incidence of bleeding after the eighth day of treatment without allowing for the reduction in number of patients maintained on treatment. We expressed the relative incidence of bleeding on each day of treatment as a proportion of the number of patients still receiving dicumarol on that day. When this necessary allowance was made, the

TABLE 1.—*Comparison of Range, Mean and Median of Prothrombin Time for a Control Group and a Group of Patients Having Major and Minor Hemorrhages*

Day of treatment	Number of Cases			Prothrombin time in seconds								
				Range			Mean			Median†		
	Control*	Hemorrhage		Control	Hemorrhage		Control	Hemorrhage		Control	Hemorrhage	
		Minor	Major		Minor	Major		Minor	Major		Minor	Major
2	57	4	3	17– 41	20– 25	28– 34	24	23	30	23	23	30
3	99	7		18– 90	31– 59		37	46		24	45	
4	96	6	2	19– 88	28– 76	80–110	40	55	95	39	53	
5	87	12	7	20– 94	28– 82	36–160	41	44	86	38	37	74
6	88	13	10	19– 81	27–120	29–122	37	47	53	34	36	43
7	67	12	5	22–129	24– 85	35–126	38	40	60	36	35	47
8	70	19	7	19–168	23–141	27– 94	38	49	53	35	38	48
9	58	15	3	18–150	22–159	31–240	37	43	102	34	33	75
10	43	6	1	18–142	22– 88		38	41	34	35	35	44

* Represents 5 per cent of the total cases without bleeding.

† Represents values, above and below which there were an equal number of cases.

elative incidence of bleeding still declined rapdly after the eighth day (fig. 3).

Thus the increased incidence of bleeding bout the eighth day cannot be explained imply as the result of delayed appearance of prolonged prothrombin time and a later deline in numbers of patients receiving dicumarol. The unique incidence remains unexplained. There is an implied dissociation between daily mean prothrombin time (single-stage method) and incidence of bleeding.

The day of most frequent bleeding was not only the eighth day of treatment but also was

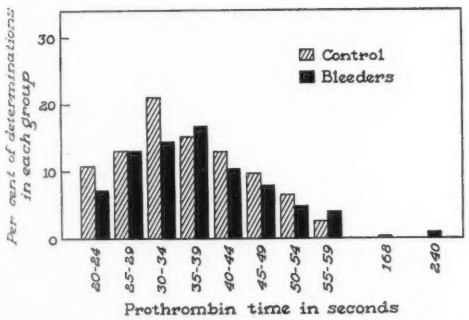

FIG. 2. The percentage incidences of various prothrombin times, given separately for the two groups. For the controls, percentage incidence of all prothrombin times for the period under consideration is shown; for the bleeders, percentage incidence of stated prothrombin times of the day of bleeding. (Note: Only values obtained on fourth to twelfth days of treatment were included in calculating the incidence in each group.)

the tenth day after operation. This was to be expected because administration of dicumarol was started on the third day after operation in 107 of the 147 cases in which bleeding occurred. Bruzelius,[3] who began treatment on the first day after operation, observed a maximal incidence of bleeding on the eighth postoperative day. This suggests that the incidence of bleeding is related more to the duration of treatment with dicumarol than to the lapse of time after operation.

COMMENT

The foregoing factual study leads to an important question that can be answered only in part: as longer prothrombin times may not be accompanied by an increase of bleeding sufficient to prohibit use of dicumarol, are we justified in demanding repeated prothrombin determinations as an obligatory prerequisite to dicumarol therapy? A more universal clinical use of dicumarol, sought to combat the ubiquitous threat of intravascular thrombosis, will remain unrealized when use depends on availability of repeated reliable prothrombin determinations. In spite of this pressing consideration, two aspects of therapy suggest continued dependence on prothrombin determinations.

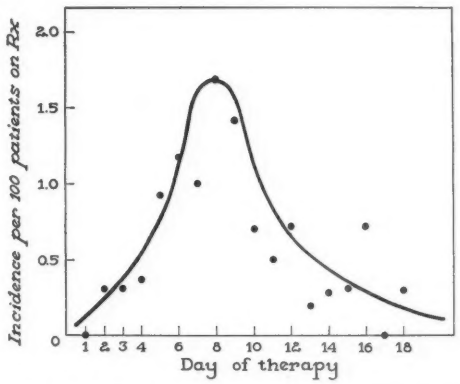

FIG. 3. Daily incidence of bleeding as a proportion of patients still receiving dicumarol therapy.

The prothrombin time in response to a given dose of dicumarol is unpredictable. Use of dicumarol without prothrombin determinations exposes a patient to the hazard of bleeding without guaranteeing the present high protection against intravascular thrombosis. There is also an unverified possibility that large doses of dicumarol may, by virtue of the magnitude of the dose itself, increase the risk of bleeding, a risk not necessarily reflected by a proportionate increase of prothrombin time.[6] Therefore, until statistical technics have apportioned the risks, we must continue to advocate that dicumarol be used only when its administration is guided by repeated determinations of prothrombin time, in order that we can insure a deficiency of prothrombin sufficient to prevent intravascular thrombosis and in order that the therapeutic goal is achieved with the smallest possible dose of dicumarol. However, the physician must not disregard the fact that bleeding may occur when prothrombin times are not greatly prolonged. He must be espe-

cially alert for the appearance of postoperative bleeding of patients after the sixth day of treatment.

Summary

In general, patients who bled during the clinical use of dicumarol after operation had a higher prothrombin time than those who did not bleed.

Correlation between bleeding and prothrombin time was only approximate. Some patients bled when prothrombin time was not greatly prolonged and others failed to bleed when it was markedly prolonged. Although the extent of prolongation of prothrombin time was only a gross measure of the tendency toward bleeding, repeated determinations of prothrombin remain the guide to safe treatment with dicumarol.

Age apparently was not a factor in the incidence of bleeding.

There was maximal bleeding on the eighth day of treatment with dicumarol with a relatively high incidence between the sixth and tenth days.

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The Effect of the Dependent Position upon Blood Flow in the Limbs

By Robert W. Wilkins, M.D., Meyer H. Halperin, M.D., and Julius Litter, M.D.

The blood flow, as reflected by the arteriovenous oxygen difference, in the arms and legs is greater in the dependent position than in the horizontal position. The physiologic and clinical significance of this finding is discussed.

THE RELATIONSHIP between the blood flow in and the position of the limbs is a matter of some clinical and physiologic interest. Clinically, it is important to know in cases of ischemic arterial disease whether the limbs have a better blood flow when they are kept horizontal on a level with the body, or are allowed to be dependent. Physiologically, it is known that when a horizontal limb is lowered into a dependent position there is an increase in local arterial (hydrostatic) pressure which is opposed (except early after dependency) by an equal increase in hydrostatic venous pressure. The arteriovenous pressure gradient, therefore, is unaltered. Nevertheless, it is possible that changes may occur in the caliber of the vessels in the dependent limb which may affect the vascular resistance and alter the blood flow. Thus, there may be passive dilatation consequent to the increased intravascular pressure, or there may be active constriction, either as a reflex or a local response to increased blood pressure or flow, or there may be complicated effects that cannot be predicted.

The measurement of changes in blood flow when a limb is lowered entails considerable technical difficulty. The use of a venous occlusion plethysmograph does not seem feasible because the veins of a dependent limb are so distended by hydrostatic pressure that they are not suitable for the further quantitative trapping of blood. Skin temperature measurements are of limited applicability because they do not reflect accurately the blood flow in the deeper tissues; they cannot be related quantitatively to blood flow in the skin; and, even as an index of directional change, they are relatively crude. Indeed, several studies of this problem by the skin temperature method have yielded conflicting results,[1–3] although all the experiments were concerned with tilting of the entire body rather than with lowering of the limb. Quantitatively reliable methods involving the use of radioactive substances for determining blood flow were not available to us at the time of this study.

The method employed in this investigation consisted of determining the arteriovenous oxygen differences. This method is based on the Fick principle that when the oxygen consumption is constant the blood flow in an extremity varies inversely as the A-V oxygen difference.

Methods

The subjects, who were hospital patients with normal circulatory systems, were studied in the basal state. The room temperature remained constant within ±0.5 degree during any given test, being between 24 C and 27 C on different days. Blood was obtained from the antecubital, femoral, or popliteal veins, on one or both sides, when the limb was horizontal, then when it was dependent, and when it was in the horizontal position again. In order to avoid repeated venipunctures with possible concomitant reflex disturbances in circulation, indwelling needles (gage 18) were employed. These were inserted under local procaine anesthesia, and were kept patent with a slow infusion of isotonic saline solution. A manometer attached to this system through a Y tube allowed frequent determinations of venous pressure to be made by the method of Moritz and von Tabora.[4]

Before each sample was collected, the infusion was disconnected and the needle was cleared of saline by withdrawing 2 cc. of blood into a separate syringe. The samples were then drawn into oiled, heparinized syringes, and immediately transferred

From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

to special containers for anaerobic storage over mercury in a refrigerator. They were analyzed for oxygen within a few hours by the technic of Van Slyke and Neill.[5] Duplicate analyses, carried out on two machines, were required to agree within 0.10 volume per cent. The arterial oxygen content was estimated from the oxygen capacity of the first venous blood sample, assuming a saturation of 96 per cent. Hematocrit determinations were done on each sample by the method of Wintrobe[6] in triplicate analyses and required to agree within 0.3 per cent. The oxygen content of each blood sample was corrected for changes in hematocrit by direct proportion to the hematocrit of the first venous sample. This excluded changes in venous oxygen content due to factors unrelated to blood flow such as hemoconcentration when the limb was dependent.

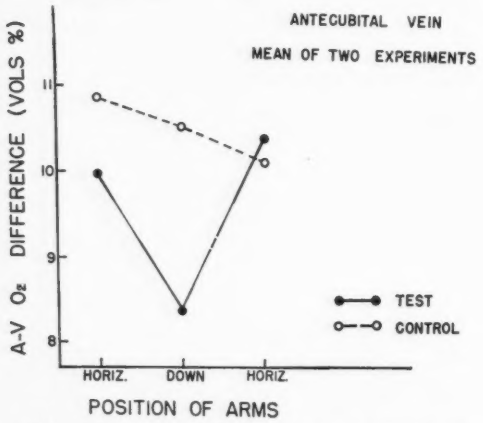

FIG. 1. The effect of the dependent position upon the arteriovenous oxygen difference in the arm. When the test arm was lowered, the arteriovenous oxygen difference increased. This was attributed to an increase in blood flow.

The procedures and results of the studies on the arms (antecubital veins) and on the legs (femoral and popliteal veins) differed in certain details, and are described separately below.

PROCEDURES AND RESULTS

Studies on the Arms

In these experiments, the subject lay on his back in a semirecumbent position. He was close enough to one edge of the bed so that one arm could be dangled. Initially, his arms were supported on Mayo tables so that the antecubital veins were approximately at the same level as the zero reference point for systemic venous pressure. Blood pressure cuffs were applied to the wrists so that the circulation to the hands could be occluded. This was done to exclude the rather large, "spontaneous," reflex vasomotor changes which might occur in the hands and mask the desired observations in the arms. Needles were inserted into the antecubital veins, pointing distally into deep branches. The saline infusions and manometers were connected, and the patient was allowed to rest quietly for about ten minutes while measurements of venous pressure were made. The wrist cuffs were then inflated to a pressure considerably exceeding the subject's systolic arterial pressure. Three minutes later the venous pressures were measured and blood samples were collected from both arms, after which the wrist cuffs were deflated. The experimental arm was then allowed to hang down beside the edge of the bed so that the fingertips were about twenty-two inches and the antecubital fossa about eight inches (depending on the length of the arm) below their original levels. When the arm had been dependent for two to four minutes the wrists were occluded. Three minutes later venous pressures and blood samples were again obtained. Finally, the arm was replaced to its original position, and the same procedure was carried out five to seven minutes later. Great care was taken at all times to keep the muscles free of tension, so as not to increase their metabolism.

Four experiments of this kind were performed. The results of two are presented in figure 1. In the other two, similar results were obtained in the experimental arm, but technical difficulties resulted in failure to obtain the control samples. It was, therefore, deemed best to exclude these experiments because it is known that such fluctuations in A-V oxygen difference may occur spontaneously in the horizontal forearm. It has been shown in this laboratory that such random fluctuations tend to be parallel in the two forearms, with a correlation coefficient as high as +0.93.[7] Therefore, one side can be used as a control for the other, and indeed must be so used when the number of observations is small.

The results of the first experiments, illustrated in figure 1, show that during dependency the A-V oxygen difference in the limb decreased

from a level of 10.0 to 8.4 volumes per cent, corresponding to a 16 per cent increase in blood flow. When the arm was returned to its original position, the A-V oxygen difference returned to 10.4 volumes per cent. Meanwhile, the control arm showed only small changes, at times opposite to those in the experimental arm. No more experiments were done on the arm since this problem is important principally as applied to the legs, and since the results in the arms and legs proved to be similar.

The venous pressures relative to the fixed (zero) level of reference were not altered appreciably in the dependent position. Relative to the level of the needle, the pressure was, of course, elevated by the hydrostatic difference. The pressures dropped about 1 cm. of saline when the hand circulation was occluded, and rose 4 to 5 cm. during the reactive hyperemia in the hand following restoration of its circulation.

Studies on the Legs

Two groups of experiments were done on the legs, the first being on the femoral veins because of the ease with which they may be punctured. As shown below, this method proved unsatisfactory for our purpose. The second method, utilizing the popliteal veins, was therefore substituted.

1. Femoral Veins. In general, the procedure was similar to that in the preceding experiments. The differences were as follows. The subject lay supine on a special bed which had a hinged section under each leg. This allowed either leg to be lowered, flexion occurring at the knee to an angle of about 60 degrees from the horizontal. Needles were inserted into both femoral veins. Blood pressure cuffs, applied on the ankles, allowed the circulation to the feet to be occluded for three minutes prior to each sampling of blood.

At first, experiments were done with the subjects lying flat on the bed. The results of one such test are shown in figure 2. They were contrary to what had been expected on the basis of the results on the arms. When either leg was lowered, the A-V oxygen difference in that leg rose. This indicated that there was either a *decrease* in blood flow, or an increase in oxygen consumption in the area through which the sample of blood had circulated. A third possibility was that a variable amount of blood from the pelvis had been drawn back into the femoral vein by the sampling syringe, contaminating the samples. Other experiments carried out in this fashion yielded similar results. At this point, it was noted that when a leg was lowered some tension could be felt in the quadriceps muscles of the thigh. Either increased oxygen

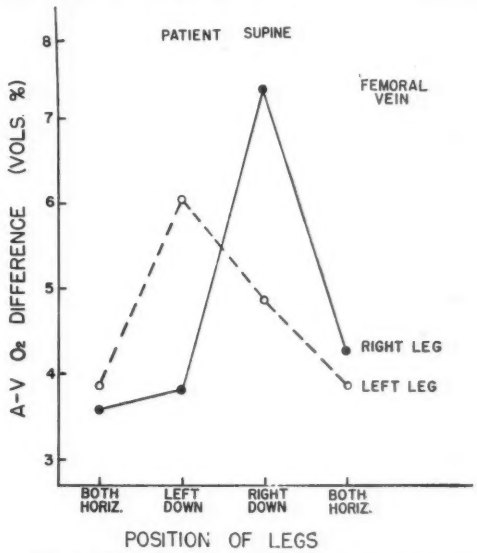

FIG. 2. The effect of dependency of the leg upon the arteriovenous oxygen difference in the femoral vein with the patient supine. When either leg was lowered, the oxygen content of the femoral venous blood from that limb was decreased, and the arteriovenous oxygen difference increased. This was assumed to be due to tension in the thigh muscles which increased their oxygen metabolism (see text).

consumption or a decreased blood flow in these slightly tense muscles could, therefore, account for the increased A-V oxygen difference, although the magnitude of the change (almost double in some instances) was surprising. The fact that the change in A-V oxygen difference indeed did occur in the horizontal thigh, and not in the dependent leg, was confirmed in an experiment carried out in exactly the same fashion, except that the circulation to the dependent leg was occluded by inflation of a cuff above the knee at greater than systolic pressure.

Further experiments on the femoral vein were carried out with the subjects supported in a semirecumbent position. It was found that in this position there was less tension in the thigh muscles when the knee was flexed, and therefore it was thought that the increased A-V oxygen difference in these muscles might be avoided. Figure 3 shows the results of one such experiment. Here, it is seen that when the test leg was lowered there was a considerable *decrease* in A-V oxygen difference as compared with the control leg. This would suggest an

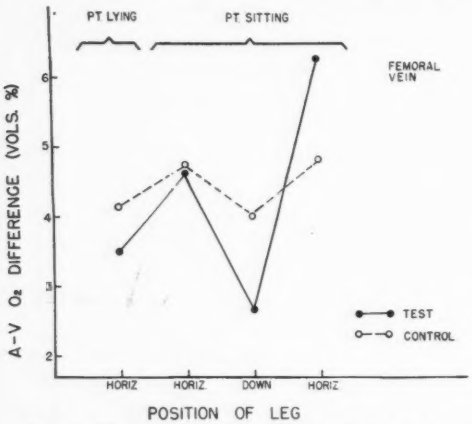

FIG. 3. The effect of dependency of the leg upon the arteriovenous oxygen difference in the femoral vein. The patient was sitting, so as to prevent tension of the thigh muscles when the test leg was dependent. The arteriovenous oxygen difference decreased when the test leg was lowered, and increased when it was again elevated to the horizontal level. This was attributed to a greater blood flow in the dependent position.

increase in blood flow in the dependent leg. Several additional tests showed similar results, but tension in thigh muscles could not always be avoided completely and occasional erratic changes in A-V oxygen differences were noted. This method, therefore, was abandoned in favor of studies on the popliteal veins.

2. Popliteal Veins. These experiments were carried out with the patient lying prone on the special bed with his groins over the hinges, so that an entire leg and thigh could be lowered, flexion occurring at the hip. An attempt was made to place indwelling needles in both popliteal veins.

Due to technical difficulties, it was usually possible to place correctly only one needle. Therefore, control observations could not be obtained in the opposite limb during most of the experiments. However, a sufficiently large number of unilateral experiments was carried out to insure that the spontaneous fluctuations in opposite directions would tend to cancel each other.

In general, the procedure was similar to that previously described. In most instances, when only one popliteal vein could be punctured, blood samples were obtained alternately with the leg horizontal, and when it was lowered to about 60 degrees from the horizontal. The leg

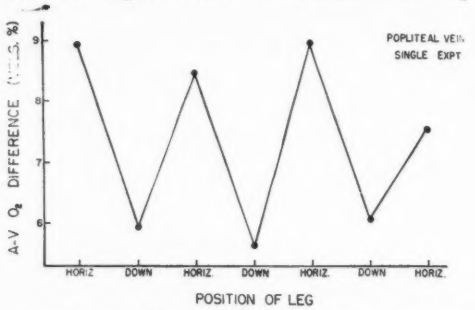

FIG. 4. The effect of dependency of the leg upon the arteriovenous oxygen difference in the popliteal vein. Each time the leg was lowered, the arteriovenous oxygen difference decreased. This was interpreted as indicating an increase in blood flow in the dependent position.

was lowered and raised three times. When samples were obtained bilaterally, the test leg was lowered and raised only once. Experiments were done with the foot excluded from, as well as included in, the circulation. Five minutes elapsed between each change in limb position and the sampling of blood. Great care was taken at all times to keep the patient comfortable and relaxed.

Figure 4 shows the results of one typical experiment. Each time the limb was lowered, the A-V oxygen difference decreased considerably. Conversely, each time the leg was brought back to the horizontal, the A-V oxygen difference rose. This would indicate that the blood flow was greater when the limb was dependent than when it was horizontal.

Experiments were carried out on a total of

1: subjects. The effects of lowering the limb was observed 25 times, and that of re-elevating it to the horizontal position, 22 times. The individual results are shown in table 1. The means show a decrease in A-V oxygen difference from 8.8 to 7.6 volumes per cent when the limb was dependent, corresponding to a 13.6 per cent increase in blood flow. Conversely, when the limb was elevated again to the horizontal position the mean A-V oxygen difference rose from 7.7 to 9.0 volumes per cent, representing a 17.5 per cent decrease in blood flow. These changes were highly significant statistically (P less than 0.01).

When the data from the experiments excluding the foot circulation were analyzed

TABLE 1.—*The Effect of the Position of the Leg on the Arteriovenous Oxygen Difference in the Popliteal Vein*

	Effect of Lowering from Horizontal to Dependent			Effect of Elevating from Dependent to Horizontal		
	A-V O_2 Difference Before	A-V O_2 Difference After	Change (% of Initial Value)	A-V O_2 Difference Before	A-V O_2 Difference After	Change (% of Initial Value)
	ml./100 ml.	*ml./100 ml.*		*ml./100 ml.*	*ml./100 ml.*	
Foot Circulation Occluded						
Patient #16	6.51	5.69	−12.6	—	—	—
	6.75	7.55	+11.9	7.55	6.79	−10.1
Patient #18	11.55	10.09	−12.6	10.09	10.52	+4.3
	10.52	7.24	−31.2	7.24	10.70	+47.8
	10.70	11.79	+10.2	11.79	11.65	−1.2
Patient #19	9.15	8.48	−7.3	8.48	9.38	+10.6
	9.38	9.12	−2.8	9.12	10.88	+19.3
	10.88	9.88	−9.2	9.88	11.46	+16.0
Patient #22	8.93	5.97	−33.2	5.97	8.47	+41.9
	8.47	5.65	−33.3	5.65	8.98	+58.9
	8.98	6.10	−32.1	6.10	7.57	+24.1
Patient #24	7.54	7.58	+0.5	7.58	6.54	−13.7
Patient #25	7.59	6.48	−14.6	6.48	8.54	+31.8
	8.54	4.06	−52.4	4.06	7.68	+89.2
	7.68	8.61	+12.1	8.61	8.10	−5.9
Patient #27	7.70	8.27	+7.4	8.27	8.86	+6.6
Patient #29	8.09	8.43	+4.2	8.43	9.11	+8.1
	9.11	7.95	−12.7	7.95	10.52	+32.3
	10.52	7.18	−31.7	—	—	—
Mean	8.88	7.69	−12.6	7.84	9.16	+21.4
Foot Circulation Included						
Patient #26	10.68	8.26	−22.7	—	—	—
	9.06	8.40	−7.3	8.40	9.75	+16.1
Patient #27	7.50	6.87	−8.4	6.87	7.52	+9.5
Patient #28	7.35	5.70	−22.5	5.70	7.63	+33.9
	7.63	6.44	−15.6	6.44	8.54	+32.6
	8.54	7.85	−8.1	7.85	8.89	+13.2
Mean	8.46	7.25	−14.1	7.05	8.47	+21.1
Mean of Combined Group	8.77	7.59	−13.0	7.66	9.00	+21.2
Standard Error	±0.278	±0.336	±3.29	±0.369	±0.313	±5.13
Significance of Difference (P)*	less than 0.01			less than 0.01		

* P represents the probability that the observed difference might be due to chance. Values of 0.05 are considered significant, and 0.01 highly significant.

separately from those including the foot (see table 1), the results for the two groups were similar. There was, therefore, no evidence from these experiments that the circulation in the foot behaved differently from that in the leg in response to the changes of position.

Only nine contralateral control observations were made during changes in position of the test leg. These showed no significant alteration in A-V oxygen difference (mean 6.9 volumes per cent before and 7.0 volumes per cent after the test leg was lowered). Thus, the fluctuations on the control side appeared to be of a random nature and cancelled each other.

As in the arm, there were no significant or consistent changes in venous pressure as referred to the fixed reference level. Thus, the rise in local pressure in the veins roughly equalled the hydrostatic difference in level, and did indeed oppose the hydrostatic increase in arterial pressure, at least by the time accurate measurements could be obtained with the method used.

The hematocrit determinations showed an average increase of 1.5 units during dependency, revealing a considerable degree of hemoconcentration in the venous blood issuing from the dependent limb. If this had not been corrected for, the higher venous oxygen contents associated with this hemoconcentration would erroneously have been attributed to a greater increase in blood flow.

Discussion

Two significant findings may be noted in these studies. The first is the increase in blood flow which occurs in a dependent limb. It was shown by Scheinberg and his co-workers[8] that if a foot is previously emptied of blood by external pressure, its blood flow during the first few seconds of dependency is greatly increased over that which would have occurred in the horizontal position. In their plethysmographic study the hydrostatic venous pressure normally opposing the increased arterial perfusing pressure in the dependent limb was temporarily eliminated by first emptying the foot of its blood. They noted that the blood flow in the emptied foot was usually *more* than doubled when the mean arterial pressure (and arteriovenous pressure gradient) was doubled, indicating the possibility of vasodilatation (decreased resistance to flow). However, they felt that their methods of recording mean arterial pressure and blood flow were too crude to permit them to attach significance to this discrepancy. The present study shows that even when the arteriovenous pressure gradient is not changed, the blood flow is greater in the dependent limb. This must be attributed to vasodilatation, probably as a passive effect of the increased intravascular pressure. It should be emphasized that in the present study the position of only the limb was changed, not of the whole body, as takes place on a tilt table or a Sanders oscillating bed. It is known that when the body as a whole is tilted into a vertical position reflex vasoconstriction occurs in the lower parts, otherwise the patient shows orthostatic hypotension. The net effect of this reflex vasoconstriction plus the passive dilatation certainly must be different from the results described here.

The second point to be emphasized is the large *increase* in A-V oxygen difference produced by even slight muscular tension, such as occurred in the thigh during dependency of the leg in the femoral vein experiments. This is attributed chiefly to an increased oxygen consumption in the tense muscles, although, of course, a change of blood flow in them cannot be ruled out. This effect outweighs any possible increase in blood flow and results in a considerable decrease in venous and tissue oxygen tensions. To increase the oxygen tension in the tissues would seem to be a most important aim of therapeutic measures in peripheral vascular disease. Any postural maneuver designed for this purpose apparently must be accomplished in such a way as to avoid the slightest muscular tension; certainly active motion as in Buerger's exercises would seem undesirable. Studies of the effects of such maneuvers are not adequate if blood flow alone is measured, without taking into account oxygen consumption. Arteriovenous oxygen differences afford a measure of blood flow in relation to metabolic demand for

oxygen, and hence are of fundamental importance.

It is frequently observed clinically that patients with ischemic vascular disease prefer to lower their limbs into a dependent position. The results of this study offer an explanation for this observation. Other patients, especially those with superimposed infection, have greater pain when the limb is dependent. This might be due to vascular distention in the inflamed area.

Summary

The blood flow in a limb (leg or arm) of a recumbent person is about 15 per cent greater in the dependent position than in the horizontal position. This was shown by measuring arteriovenous oxygen differences in the antecubital or in the popliteal vein. If the dependent position is accompanied by muscular tension in the limb, however, the oxygen content of the venous blood may decrease markedly, due presumably to increased local oxygen consumption.

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Cholesterol, Cholesterol Esters and Phospholipids in Health and in Coronary Artery Disease

II. Morphology and Serum Lipids in Man

By MENARD M. GERTLER, M.D., STANLEY MARION GARN, PH.D. AND HOWARD B. SPRAGUE, M.D.

Employing the Sheldon method of physique classification, it has been shown that a definite relationship exists between the various physiques and the level of lipids in the serum of a coronary disease group and a control group. Positive correlations existed between endomorphy and serum lipids, negative correlations existed between ectomorphy and serum lipids. There were negligible correlations between mesomorphy and the serum lipids. Intragroup comparison in the coronary disease patients showed that the general trend of endomorph-ectomorph differences continued, but that the lipid values in coronary mesomorphs were higher than in the coronary endomorphs.

THE STUDIES in the past relating physique and serum lipids have been suggestive of such a relationship. However, the differences in physique classifications and nomenclature have made it virtually impossible to compare the results. Gildea, Kahn, and Man[1] have shown that pyknic individuals possess to a significant degree a higher level of serum cholesterol than do intermediate and leptosomatic individuals. McQuarrie has shown the presence of hypolipemia in schizophrenics[2] (who are generally of asthenic or leptosomatic habitus[3]). Similar observations were made by Miassnikow[4] and Tschernorutzky[5] who found, on blood analysis, that hypersthenics and asthenics showed a tendency to hypercholesteremia and hypocholesteremia, respectively. Other observers maintain that there is an association between the level of serum cholesterol and increase in weight or degree of "obesity."[6,7] The general trend is, therefore, to admit an association between avoirdupois and serum cholesterol. However, it is disconcerting that, because of their unavailability, careful laboratory technics comparable to the accuracy of the chemical determinations could not be applied to the morphologic classification of the individuals. If such had been available, not only would the value of the previous work have been enhanced, but corroborations would have been facilitated.

The constitutional typology in the past studies have been classified by loose and ill-defined terminology. Some observers have used the terms "obese" and lean."[6] Others presented a tripolar system with indefinite poles, "obese, medium and lean."[7] Still others have followed Kretchmer's terminology but not his anthropometry with a tripolar classification of pyknic, intermediate, and leptosomatic.[8] At best, the systems are not mutually intelligible, and at worst, the variations in personal error, in standards, in age, and other changes limit the accuracy of the interpretation and make comparative ratings difficult. It is important to stress that despite these difficulties and theoretic objections, consistent and gross differences have emerged.

In order to minimize the difficulties just enumerated, but without placing undue stress on ratios, indices, or scales of "build," the Sheldon[9] system of body build rating, "somatotyping," was finally selected for use in this work. Our reasons for selecting this system are (1) it avoids the immediate categorization

From the Coronary Research Project, Cardiac Department, Massachusetts General Hospital and Harvard Medical School. Drs. P. D. White, H. B. Sprague, E. F. Bland, J. Lerman, S. A. Levine, and E. A. Hooton, Directors. Supported by a grant from the Commonwealth Fund, New York City.

into types, though as few or as many "types" can later be set up as is necessary or consistent with the data; (2) it is an extensively used system, having been treated since its inception in three major works, nearly 50 papers, and in several doctoral theses; (3) the system possesses maximum communication value and (4) rating is done numerically with equal interval-scales and is therefore susceptible to mathematical treatment, statistical analysis and correlation technics. Additional details are found in the references listed in the bibliography.

In the Sheldon system, the numerical score represents the relative predominance of each of the three components or "directions" of physique. The minimum value in any component is 1, the maximum 7, and the modal value 4. Thus, a 4-4-4 describes a mid-range physique; the components are, briefly:

1. First Component. *Endomorphy*, softness of contour and roundness, smallness of peripheries, without musculature or linearity.

2. Second Component. *Mesomorphy*, angularity and muscularity, breadth of shoulder, muscularity of legs and arms, squareness of contour, strength of build.

3. Third Component. *Ectomorphy*, linearity of physique, elongation, flatness anterioposteriorly, long peripheries.

Thus, a rating of 2-4-5 in this system refers to an individual who shows a relative predominance in linearity, but with good musculature and bony development, and near minimum softness and roundness.

Further considerations of this system are: (1) The primary record is photographic and subject to revision as necessary. (2) Any number of people can collaborate on or check the ratings. (3) The system is developed as an age-correctable system so that individuals of similar habitus but differing age can be compared. (4) The system of rating must be done in conjunction with, not in the absence of, previous health and other data; the somatotype system is an attempt to express the constitutionally determined body build.

The establishment of correlations of significant value between bodily habitus and serum lipids such as cholesterol (total and free), cholesterol esters, and phospholipids, should lead to the determination of more definitive normal lipid values and perhaps offer a clue to abnormal lipid metabolism in the lipodystrophies. (Currently, the terms hypolipemia and hyperlipemia are at best statistical concepts, derived from populations without any attempt to classify the physiques.) Accordingly, an individual value considered pathologic may be within the physiologic range for that particular body habitus. Since the physical constitution is predetermined to a large degree, it is reasonable to suppose, without postulating a causal relationship, that the chemical attributes likewise seem to be predetermined genetically. Hence, an attempt to associate physique and serum lipids has a certain theoretic justification.

Materials and Methods

Blood was collected and treated as described in the first paper[10] of this series, from 146 healthy active working men in a Cambridge industrial concern, and from 97 men who had experienced myocardial infarction prior to the age of 40. It has been shown that the two groups were of comparable age at the time of examination.[11]

At the time of examination, standardized "somatotype" photographs were made of each individual, photographing three views (front, side and rear) in the manner and pose described by Sheldon. The men were measured anthropometrically, inspected visually at the time of measurement and questioned as to their degree of activity and athletic training. From the original impressions, from the measurements, from the data on age and health history, and from the somatotype photograph, a final numerical rating was assigned to the individual which expressed as nearly as possible our judgment as to his constitutional body-build or "somatotype."

The principal question arises as to whether we have mistaken nurture for nature (i.e., whether we have been biased by age-influenced deposits of fat). Were this true we should get significant positive correlations between age and endomorphy, and negative correlations between age and mesomorphy and age and ectomorphy. As shown previously by us[11] the actual correlations are statistically insignificant, being $+.04 \pm .08$, $-.03 \pm .07$ and $-.06 \pm .08$, respectively. We assume then, that our physique rating system is uninfluenced by age.

Relationships between physique and serum lipid levels were explored in two ways, (1) by computing the coefficient of correlation between each of the three components and the various lipids, and (2) by comparing the lipid levels of individuals grouped according to physique.

The correlation of coefficient (r) gives results varying between −1.0 and +1.0, the former being a perfect negative correlation, and the latter being a perfect positive correlation. In such a study as the present, however, there are interfering factors of age, etc., so that correlations near −1.0 or +1.0 are usually not attained; also highest correlations are obtained when there is a full spread of both variables; in the present case there are not many extreme physiques.

Results

1. *Serum Lipids Compared with Height, Weight and Ponderal Index (Height over Cube Root of Weight)*

The data were first explored by the use of the correlation coefficient to see whether there were correlations between gross weight, absolute height, ponderal index (the height-weight index of body build) and serum lipids (fig. 1). This was done, in part, to check some earlier statements that serum lipid levels were functions of body weight. The height-weight index was chosen as the best present simple numerical measure of body massivity (for a discussion of this measure see Sheldon[9]; McCloy[13]; Krogman[14]; and Pearl[15]).

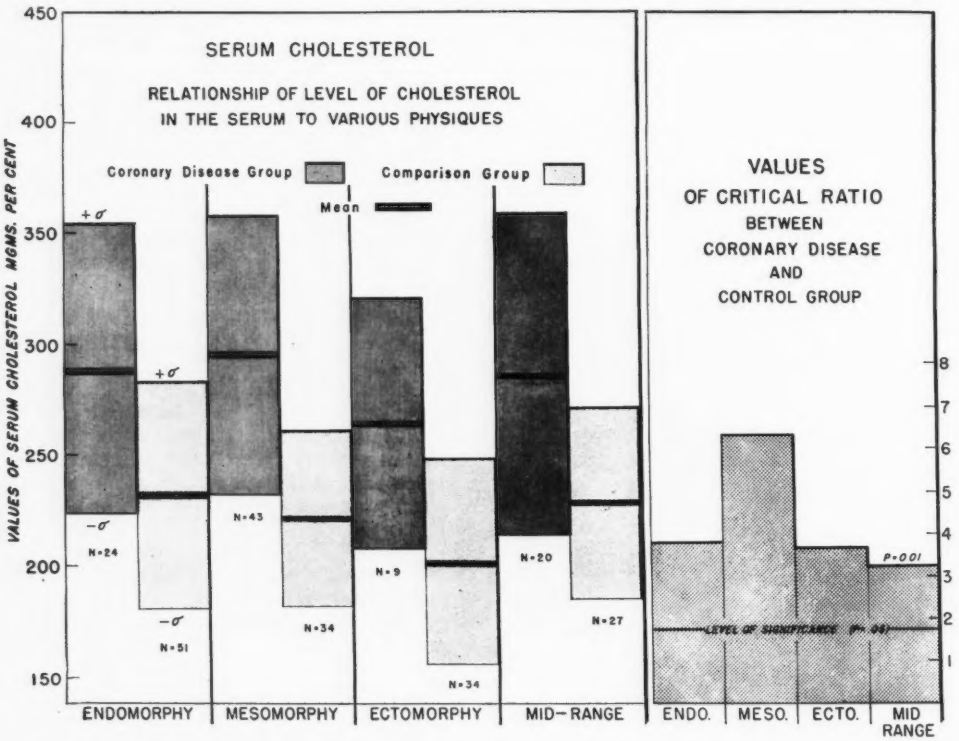

FIG. 1. The observed levels of serum cholesterol in the various physiques of the control group and the coronary disease group.

We have also compared among themselves the serum lipid levels of dominant endomorphs, mesomorphs, ectomorphs, and mid-range physiques; calculating the difference in each case, and the significance of the difference by the appropriate statistical formulas. (For further details see paper number I in this series.)

In all cases, significant correlations or differences are marked + and highly significant differences or correlations are marked ++. The plus figures equal the .05 level of confidence, and the double-plus figures equal the .01 level of confidence, or better (see the first paper in this series[10] and Fisher[12]). Nonsignificant issues are marked N.S.

The correlation values show clearly that no significant correlation exists between the level-

of total cholesterol and phospholipids in the serum, and weight alone or stature alone. Accordingly, it is reasonable to state that these gross factors are not immediately involved in the problem. On the other hand, the relationship between these two lipids and the ponderal index reveals the following: (1) The correlations are larger than the independent correlations. (2) A negative correlation in both instances, which indicates that the levels of both cholesterol (total) and phospholipids in the serum decreases as the individual becomes more linear. (3) The correlation between serum phospholipids and ponderal index is statistically significant but not of predictive value.

TABLE 1.—*Correlation between Total Cholesterol and Phospholipids and Weight, Height and Ponderal Index*

Correlation	Correlation and Standard Error	Significance
Cholesterol and weight	+.06 ± .08	n.s.
Cholesterol and height	−.06 ± .08	n.s.
Cholesterol and ponderal index	−.12 ± .08	n.s.
Phospholipids and weight	+.17 ± .08	+
Phospholipids and height	−.07 ± .08	n.s.
Phospholipids and ponderal index	−.21 ± .08	+

Phospholipids in this paper are expressed as lecithin, which is considered to be 25 times the serum lipid phosphorus level.

The cholesterol values show a higher correlation with the ponderal index than with either height or weight alone. Thus, as the measure of body build is refined, the correlation approaches significance. Accordingly, it is reasonable to expect that with a more refined measure of physique such as the Sheldon rating, the correlations should become more useful.

2. *Serum Lipids and the Sheldon Components*

The data were further explored by computing the relationships between each of the three components of physique (rated on a 1–7 scale) and the lipid levels; it is to be noted that the Sheldon method of rating components on an equal-interval scale of progression is the first technic of body typing that can be used in computing such correlations.

Table 2 shows (1) significant correlations between all lipids and endomorphy, (2) insignificant correlations between all lipids and mesomorphy, and (3) significant negative correlations between all lipids and ectomorphy. Thus, we see that the correlations are higher than they were with the height-weight ratio, and that the Sheldon components are therefore closer to the factors involved than are the ratios. The lack of a significant correlation between any lipid and mesomorphy may be due in part to the fact that this component of physique has not been separated adequately from the other components; thus, the relationship between each of the components as expressed above has not been entirely separated from the combining effects of the other two. This is accomplished as well as possible in the following sections.

TABLE 2.—*Correlation between the Levels of Total Cholesterol, Cholesterol Esters, and Phospholipids in the Serum and the Sheldon Components*

Lipid	Endomorphy	Mesomorphy	Ectomorphy
Cholesterol	+.26 ± .08++	+.01 ± .08	−.18 ± .08+
Cholesterol esters	+.24 ± .08++	+.04 ± .08	−.20 ± .08
Phospholipids	+.23 ± .08++	+.05 ± .08	−.21 ± .08+

+ Significant
++ Highly significant

3. *Mean Lipid Levels of Various Physique Groups*

Since the relationships between both endomorphy and ectomorphy and the lipids have been established on the basis of the correlation coefficient, it becomes necessary to see whether individuals grouped on the basis of physique will exhibit statistically significant differences in mean lipid levels. In other words, will endomorphs, mesomorphs and ectomorphs differ to a statistically significant degree from each other in their lipid levels? To accomplish this, the total comparison group of 146 was divided into (1) endomorphic dominances, (2) mesomorphic dominances, and (3) ectomorphic dominances,

while the somatotypes 3-3-4, 3-4-3, etc. were classed as mid-range somatotypes. Thus, there are four gross groups for comparison—Endomorphs, Mesomorphs, Ectomorphs, and Mid-range physiques. In the original data the dominances were further broken down into primary and secondary dominances, but this is not done here because of space considerations. The results are shown in table 3.

TABLE 3.—*Means and Standard Errors of the Serum Lipids of the Various Physiques within the Control Group*

	Free Cholesterol	Cholesterol Esters	Total Cholesterol	Phospholipids
Endomorphs	101.55 ± 4.14*	133.08 ± 4.85	234.63 ± 6.62	311.31 ± 5.82
Mesomorphs	104.29 ± 4.41	119.03 ± 4.10	223.32 ± 6.24	300.29 ± 6.02
Ectomorphs	96.82 ± 4.57	110.97 ± 4.37	207.79 ± 6.05	281.15 ± 6.35
Mid-Range	94.00 ± 5.59	133.44 ± 6.27	227.44 ± 8.18	298.33 ± 7.51
Total	99.69 ± 2.33	124.73 ± 2.60	224.42 ± 3.53	299.32 ± 3.33

* Mean value and standard error of the mean.

TABLE 4.—*Significances of the Differences between Means among the Various Physiques and the Various Lipids in the Normal Group*

	Endo. vs. Mesomorph	Endo. vs. Ectomorph	Endo. vs. Mid-Range	Meso. vs. Ectomorph	Meso. vs. Mid-Range	Ecto. vs. Mid-Range
Free Cholesterol	n.s.	n.s.$\overset{f}{\frown}$	n.s.$\overset{f}{\frown}$	n.s.$\overset{f}{\frown}$	n.s.$\overset{f}{\frown}$	n.s.$\overset{f}{\frown}$
Cholesterol esters	+	++	n.s.	n.s.	+	+
Total cholesterol	n.s.	++	n.s.	+	n.s.	+
Phospholipids	n.s.	++	n.s.	+	n.s.	+
Total significant	1	3	0	2	1	3
Total not significant	3	1	4	2	3	1

\+ Significant, i.e., critical ratio greater than 2.0.
++ Highly significant, i.e., critical ratio greater than 3.0.
n.s. Not significant.
$\overset{f}{\frown}$ *f* test.

The data in table 3 confirm and extend the findings made by the use of the correlation technic. In all four lipids, free cholesterol, cholesterol esters, total cholesterol, and phospholipids, the mean values for endomorphic dominances are higher than the mean values for ectomorphic dominances. In two out of four instances (total cholesterol and phospholipids) the mean values for endomorphs are the absolute highest; in one instance (free cholesterol) the mesomorphs are absolutely (but not statistically) the highest. In one instance (cholesterol esters) endomorphs and mid-range physiques are equal.*

A somewhat better picture of the total lipid level of the serum is obtained by adding total cholesterol to phospholipid values in all of the four subgroups mentioned. The results for the endomorphs, mesomorphs, ectomorphs and mid-range physiques are in order: 545, 523, 489, and 526 mg. per cent. In order of descending lipid level, they are endomorphs, mid-range physiques, mesomorphs and lastly ectomorphs. In this instance, the ectomorphs are approximately 10 per cent below the endomorph levels.

In table 4 the differences and their significances have been computed so that the differences between the values shown in table 3 will become more meaningful.

* The mean endomorphy in the mid-range physique is approximately 4.00 as compared to a mean of approximately 5.00 for the dominant endomorphs.

The test of significance eliminates many of the apparent differences; only the plussed values in table 4 represent the statistically significant differences. In general, the observation is again made that the ectomorphs differ most radically from the rest of the group so that 8 of the 10 statistically significant differences on the table include ectomorphy in some combination. The difference between endomorphy and mesomorphy is apparent in the serum cholesterol esters.

TABLE 5.—*Values of Coefficients of Variation of Serum Lipids among the Various Physiques of the Control Group*

	Free Cholesterol	Cholesterol Esters	Total Cholesterol	Phospholipids
Endomorphs	29.13	26.01	20.15	13.34
Mesomorphs	24.65	20.09	16.30	11.69
Ectomorphs	27.50	22.94	16.99	13.18
Mid-Range	30.90	24.43	18.70	13.07
Total	28.29	25.19	18.98	13.44

cal mean values, yet one may be much more variable than the other. The less variable group is said to be, from a statistical point of view, more homogeneous. In the present study the problem of predictability and variability are closely connected for we would expect minimum predictability in a highly variable group and maximum predictability in a homogeneous group. Accordingly, and as seen in tables 5 and 6, variances were compared through the coefficient of variation and comparison of the standard deviations (sigma).

The comparison of variances shows that in all four lipids the mesomorphs are absolutely least variable in their lipid levels; the endomorphs are most variable (three out of four lipids) and the mid-range physique is the most variable in free cholesterol.

As shown in table 6, the coefficient of variation is in every case lower for the mesomorphs than the endomorphs and the standard deviation is as well (table 6). Though the mesomorphs have absolutely lower variance, the differences

TABLE 6.—*Comparison of Variances in the Control Group Standard Deviations ± Standard Errors*

Lipid	Endomorph	Mesomorph	Ectomorph	Mid-Range	Total
Free Cholesterol	29.58 ± 2.93	25.71 ± 3.12	26.63 ± 3.23	29.05 ± 3.95	28.20 ± 1.65
Cholesterol Esters	34.61 ± 3.43	23.92 ± 2.90	25.46 ± 3.09	32.60 ± 4.44	31.42 ± 1.84
Total Cholesterol	47.27 ± 4.68	36.41 ± 4.42	35.30 ± 4.28	42.52 ± 5.78	42.60 ± 2.49
Phospholipids	41.53 ± 4.11	35.10 ± 4.26	37.05 ± 4.49	39.00 ± 5.31	40.22 ± 2.35

In order to determine whether the differences shown might have been due to age differences, the mean ages of the physique grouping were determined and shown not to vary appreciably from each other. Thus, the mean ages for endomorphs, mesomorphs, ectomorphs and mid-ranges are 39.33, 36.95, 38.11, 39.80 years respectively. Accordingly, the significant differences that occur in the lipid levels between the various physiques are real differences and uninfluenced by age differences.

4. Comparison of Variances

Two groups may differ, not only in the absolute mean values, but also in the degree of variability. Thus two groups may have identi-

attain the statistical significance level only in the cholesterol esters. However, it is reasonable to state that the mesomorphs are absolutely as well as relatively less variable in their serum lipids. (This is a statement of statistical variability and should not be construed to mean that the individual is more or less variable from day to day.)

While these figures have pertained to the normal group, the data may now be considered from the series of 97 young men who have experienced coronary artery disease prior to the age of 40. From previous papers it was shown that the group was characterized biochemically by a serum cholesterol level approximately one standard deviation above the

normal mean, and in morphology by comparably elevated mesomorphy and diminished ectomorphy. One asks, therefore, whether the biochemical difference between the coronary and the noncoronary group could be explained on the basis of physique alone.

5. Lipid Metabolism in the Coronary Group Corrected for Physique Differences

As has been shown in previous papers in this series,[10, 11] and in other publications,[16] the group of young males with coronary artery disease differ from the comparison group by 62 mg. per cent in cholesterol, +.77 units in mesomorphy and −.65 units in ectomorphy. Since a correlation between physique and lipid levels has been demonstrated in this paper, one may well ask whether the coronary artery disease group, drawn as it is from a distinct physique population, owes its biochemical peculiarities to the physique differences. This can be determined by the technic of partial correlation, correcting, as it were, for the differences in physique and determining in effect, what the coronary group would be like if its physique approximated the physique of the normal group.

The correlation between mesomorphy and cholesterol is +.01 ± .08 and the correlation between ectomorphy and cholesterol is −.18 ± .08. It is seen that by correcting for the differences in the second and third components, a final value of 228.57 mg. per 100 cc. is obtained. Since this does not differ enough to wipe out the large significant difference between the coronary and the comparison group, it must be concluded that the biochemical difference between the young coronary artery disease patient and the normal individual is only partly attributable to a difference in physique and a large difference not physique-associated still remains.

6. Comparison of the Coronary Artery Disease Group and the Normal Group in the Four Lipid Constituents by Physiques

The findings in section 5 may be tested in another way. In the first paper of this series[10] it was shown that the lipid levels of the coronary artery disease patient differed statistically from those of the comparison group of males, and in this paper it has been shown that for the control group the physique groupings rated in the manner of Sheldon, differed in the four lipid levels. One wonders (1) whether these differences remain in the coronary artery disease group, or (2) whether coronary artery disease wipes out the normal physique differences, or (3) whether the coronary artery disease exaggerates the difference.

TABLE 7.—*Means and Standard Errors of Serum Lipids of the Various Physiques within the Coronary Disease Group*

	Free Cholesterol	Cholesterol Esters	Total Cholesterol	Phospholipids
Endomorphs	113.50 ± 9.37*	176.00 ± 11.72	286.76 ± 12.91	310.63 ± 11.74
Mesomorphs	110.19 ± 5.08	184.21 ± 7.05	294.40 ± 9.33	319.46 ± 10.47
Ectomorphs	100.44 ± 11.52	164.11 ± 16.44	264.56 ± 19.80	328.00 ± 12.04
Mid-Range	111.56 ± 9.00	165.78 ± 15.23	279.10 ± 16.79	314.00 ± 19.04
Total	110.36 ± 3.86	176.66 ± 5.47	286.51 ± 6.59	316.42 ± 6.67

* Mean Values and Standard Error.

As shown in table 7, the marked differences exhibited by the normal group are attenuated though the trend (endomorphs have higher lipids than ectomorphs) to some extent maintained the value; thus, in the coronary artery disease group free cholesterol is 110 mg. per cent as compared with 100 mg. per cent. Cholesterol esters are 176 mg. per cent as compared with 164 mg. per cent; total cholesterol is 286 as compared with 264 mg. per cent. The phospholipids, however, are reversed; 330 as compared with 312 mg. per cent.* However, endomorphic coronary patients no longer possess

* This reversal of trend appears to be important and will be considered in another publication.

as they did in the control group, the maximum lipid levels: the mesomorphs now have the higher lipid levels in two instances, i.e., cholesterol esters and total cholesterol. In other words, some of the physique differences are obliterated within the coronary group. There is no statistical difference in the coronary artery group as between the physiques with respect to cholesterol esters. This is additional evidence to favor the viewpoint that the coronary artery disease group is a very homogeneous group.

TABLE 8.—*The Value Assumed by the Coefficient of Variation of the Serum Lipids within the Various Physiques of the Coronary Disease Group*

	Free Cholesterol	Cholesterol Esters	Total Cholesterol	Phospholipids
Endomorphs	40.45	32.63	22.51	16.47
Mesomorphs	30.21	25.09	20.77	16.72
Ectomorphs	34.40	30.07	22.46	8.21
Mid-Range	34.21	38.96	26.55	20.11
Total	33.92	30.00	22.64	16.50

TABLE 9.—*Values of Standard Deviations and their Standard Errors within the Coronary Disease Group*

	Endomorph	Mesomorph	Ectomorph	Mid-Range	Total
Free cholesterol	45.91 ± 6.63	33.29 ± 3.59	34.55 ± 8.14	38.17 ± 6.37	37.43 ± 2.73
Cholesterol esters	57.92 ± 8.29	46.21 ± 4.98	49.33 ± 11.63	64.59 ± 10.77	53.00 ± 3.87
Total cholesterol	64.56 ± 9.13	61.16 ± 6.60	59.41 ± 14.00	75.09 ± 11.87	64.88 ± 4.66
Lecithin	51.17 ± 8.30	53.40 ± 7.41	26.93 ± 8.52	63.16 ± 13.47	52.15 ± 4.72

7. *Comparison of Variation of the Physiques within the Coronary Disease Group*

In tables 8 and 9 the coefficients of variation and the standard deviation are compared for the physique within the coronary disease group.

The mesomorphic group again is the most homogeneous group (it varies less in all lipids except phospholipids and in that instance, sampling size may be a factor). However, the mid-range group is the most variable group (in all instances except free cholesterol). The endomorphic group is the most variable in free cholesterol and the ectomorphic group is the least variable in phospholipids.

In table 9, the standard deviations and their standard errors are tabulated for each lipid and physique group.

The apparent differences in variability are best tested by the f test[12] which will determine the significance of the differences.

The only statistically significant variability existed in the free cholesterol between the mesomorphs and mid-range group. Since only one real difference occurs, it is reasonable to disregard it, for it could occur on a chance basis.

8. *Comparison of Coronary Artery Disease Patients and Healthy Comparison Males by Physique Groups*

As shown previously, the various physique groups of the normal group differ from each other in these lipid levels to statistical significance, and finally coronary artery disease patients grouped according to physique show differences in lipid levels which do not reach statistical significance.

It is possible to compare the coronary artery disease patients, grouped according to physique, to healthy males similarly grouped (table 10). In this way, the bias developing from the fact that the coronary artery disease patients show a different physique distribution may be eliminated to a great extent.

When comparisons are made on a physique basis, as tabulated in table 11, it is noted that levels of the lipids of the coronary patients exceed the values in the normal group in 10 out of 16 combinations. By groups, total cholesterol and cholesterol esters show significant differences in the endomorphic and mesomorphic groups, while the mid-range group is statistically different in all lipids except the phospholipids. In absolute values the magnitude of the differences is nearly constant in all physiques except the ectomorphs. This may be

partially accounted for on the basis of sample size.

TABLE 10.—*Means and Standard Errors of the Serum Lipids among the Various Physiques in the Coronary Disease Group and in the Control Group*

Physique Grouping	Free Cholesterol	Cholesterol Esters	Total Cholesterol	Phospholipids
Coronary endomorphs	113.50 ± 9.37	176.00 ± 11.72	286.76 ± 12.91	310.63 ± 11.74
Control endomorphs	101.55 ± 4.14	133.08 ± 4.85	234.63 ± 6.62	311.31 ± 5.82
Coronary mesomorphs	110.19 ± 5.08	184.21 ± 7.05	294.40 ± 9.33	319.46 ± 10.47
Control mesomorphs	104.29 ± 4.41	119.03 ± 4.10	223.32 ± 6.24	300.29 ± 6.02
Coronary ectomorphs	100.44 ± 11.52	164.11 ± 16.44	264.56 ± 19.80	328.00 ± 12.04
Control ectomorphs	96.82 ± 4.57	110.97 ± 4.37	207.79 ± 6.05	281.15 ± 6.35
Coronary mid-range	111.56 ± 9.00	165.78 ± 15.23	279.10 ± 16.29	314.00 ± 19.04
Control mid-range	94.00 ± 5.59	133.44 ± 6.27	227.44 ± 8.18	298.33 ± 7.51
Total coronary	110.36 ± 3.86	176.66 ± 5.47	286.51 ± 6.59	316.42 ± 6.67
Total control	99.69 ± 2.33	124.73 ± 2.60	224.42 ± 3.53	299.32 ± 3.33

On the basis of these differences, it is reasonable to contend that the coronary disease physique differentiations of serum lipids are superimposed on the normal physique differentiations without obscuring them.

From table 11 it may be seen that in all the four lipids considered, the coronary disease group exceeds the control group by statistically significant values. The greatest differentiation occurs in the mesomorphic physique grouping in total cholesterol and cholesterol esters. This point will be alluded to in the discussion.

TABLE 11.—*Significances of the Differences between the Means among the Various Physiques in the Coronary Disease Group and in the Control Group*

	Free Cholesterol	Cholesterol Esters	Total Cholesterol	Phospholipids
Endomorphs	n.s.	++	++	n.s.
Mesomorphs	n.s.	++	++	n.s.
Ectomorphs	n.s.	++	++	+
Mid-Range	+	+	+	n.s.
Total	*	++	++	+

\+ Significant
++ highly significant
n.s. not significant

11. Indicial Ratios, Cholesterol: Phospholipids

It was shown that an overall difference in the cholesterol:phospholipids ratio exists between the coronary disease group and the control group. Because of the differences which become apparent in the physique breakdown in the four lipids considered, it was decided to determine whether (a) the cholesterol:phospholipids ratio showed similar differences within the various physiques of either group, and (b) what physique group revealed the most significant differences.

Table 12 shows the cholesterol:phospholipids ratios of the various physiques in the coronary disease group and the control group.

There is virtually no difference between the physiques in the control group or the coronary disease group insofar as the cholesterol:phospholipids ratio is concerned. It is apparent that again the greatest difference between the two groups appears in the mesomorphic physique,

TABLE 12.—*Values Assumed by the Cholesterol: Phospholipids Ratio among the Various Physiques in the Coronary Disease Group and the Control Group and their Significances*

	Coronary Disease Group	Control Group	Levelof Significance
Endomorph	90.48 ± 3.80	75.20 ± 1.48	+
Mesomorph	92.48 ± 2.60	74.76 ± 1.96	++
Ectomorph	85.88 ± 8.60	74.28 ± 1.92	n.s.
Mid-Range	81.52 ± 6.04	76.28 ± 2.04	n.s.
Total	89.48 ± 2.04	75.08 ± 0.92	++

while the least statistical significance appears in the ectomorphic physique.

Discussion

These data have shown unimportant and probably chance correlations between serum lipid values and height alone or weight alone; higher and significant correlations between serum lipid values and the height-weight or ponderal index of build were evident, with the indication that massiveness of build and both cholesterol and phospholipid levels are positively correlated. Then, by employing standardized but still subjective estimates of body build rather than the index itself, it was shown (1) that somewhat higher correlations with positive correlations exist between endomorphy and both of these lipid levels; (2) that negative correlations exist between ectomorphy and both of these lipid levels, and (3) that nonsignificant correlations exist between the lipids and mesomorphy. When the three components were used for classification and four categories (dominant endomorph, dominant mesomorph, dominant ectomorph and mid-range) were set up, it was shown that the mean value of all the lipids considered (except free cholesterol) was highest in the endomorphs, lowest in the ectomorphs, and somewhat higher in the mid-range group than in the dominant mesomorphs. The magnitude of these differences was relatively great (table 4). The mean difference between dominant ectomorphs and dominant endomorphs was approximately equal to one standard deviation; in other terms (as we have shown) the difference between the two groups approximated a 15 year age difference.[17]

There is an association between all four lipid levels and physique, not only in the normal healthy "comparison" males, but also in the presence of coronary artery disease and despite the higher serum lipid levels in the latter case. The basic pattern reveals itself in both groups, that the more massive the physique the higher the lipid levels, and the more linear the physique the lower the lipid levels. However the details of the pattern are altered in the coronary artery disease patients, and the alteration of the details provides our first important finding. In the normal group the endomorphic physiques tend to have higher lipid levels than the mesomorphic physiques, though both are higher than the ectomorphic physiques. In the coronary artery disease group this particular trend is reversed; for in the four lipids considered here, three are higher in the coronary artery disease mesomorphs and one (free cholesterol) significantly lower. Therefore, when the two groups are compared by physique, the mesomorphs are found to be the most differentiated. This is evidenced not only by the actual differences between the coronary mesomorphs and the control mesomorphs, but also by the observation that the mesomorphs possess the highest values of serum cholesterol. Clearly then, the coronary artery disease mesomorphs are drawn from a differentiated population.

A "coronary" threshold of cholesterol does not appear to exist; if such a threshold had to be reached before coronary artery disease manifested itself, the physique differences would have been wiped out—mesomorphs, endomorphs, ectomorphs and mid-range would have conformed to this threshold. The fact that such a condition does not exist confirms the findings in the first paper of this series[10]—namely that coronary artery disease can and does exist well below the accepted limits of hypercholesterolemia and hyperlipemia although hypercholesterolemia has an undoubted association with coronary artery disease on a group, rather than an individual, basis.

If then, absolute serum cholesterol values are not the answer, what explains the constantly higher lipid levels in the coronary patients, physique by physique, and at the same time explains the continued maintenance of physique differences within the two groups?

The answer to both questions comes in part from an examination of the magnitude of the differences in table 10. For each lipid except phospholipids, the differences between the coronary endomorphs and the normal endomorphs, the coronary ectomorphs and the normal ectomorphs and the coronary mesomorphs and the normal mesomorphs are of the same order of magnitude. This suggests strongly the same conclusions that we have previously considered, namely that in coronary artery disease a spe-

cific predisposition (Pc) to the disease is superimposed on the normal lipid metabolism, and that this predisposition (Pc) is responsible for the difference. Since it could be a lipid factor, and may raise the lipid levels, many workers have decided that it is the absolute lipid level that is important. However, the evidence here indicates that an absolute (high) lipid level is important only in that it may reveal the presence of that predisposition to coronary artery disease, but with constitutionally low cholesterol levels the predisposition is hidden. Thus we find coronary artery disease in individuals with low lipid levels because it is the constant and not the absolute level that is concerned.

The Pc factor need not be primarily a difference in serum lipids, but could be due to independent additive factors. One factor might be the yet unproven concept of the difference in thickness and the permeability of the coronary arteries in mesomorphs and the other physiques. Thus, it may be that the muscular layer of the coronary artery disease patients (particularly the mesomorphs) is thicker and thereby produces a narrower lumen which is easier to obliterate by equal amounts of plaque formation. Or one may postulate that there is a difference in the permeability of the intimal tissue between the coronary disease patients and the control patients which will permit an easier penetration by the cholesterol or macrophages into the intima. Or there may be both a narrower lumen superimposed upon increased plaque formation. It is also likely that what changes have been effected by medication or diet have affected only the serum lipids that are part of the individual's "normal" level, and not the highly important part represented by the predisposition constant.

How, then, does mesomorphy fit into the picture? Predicting on the basis of the normals, endomorphs would be expected to have a higher incidence of coronary disease in youth, but they do not; mesomorphy is therefore uniquely associated with coronary artery disease, and with mesomorphy in coronary artery disease we find higher than expected lipid levels. It is likely, therefore, that the Pc factor is given full rein in the presence of this somatic component, and, although it may be present with predominant ectomorphy, it is probably at a minimum.

Summary

1. One hundred forty-six healthy, active, employed males were compared with 97 young males who had experienced a myocardial infarction prior to the age of 40, in a study of the relationships of body morphology and serum lipids in health and disease.

2. The Sheldon system of somatotyping was chosen for use because (a) it uses photographic records, (b) it is recorded numerically, (c) it is age-correctable, and (d) it has been most extensively used.

3. The correlation coefficients established between the various lipid levels and weight alone or height alone were negligible; significant correlations were established between the ponderal index and the various lipid levels.

4. Rated on the basis of the Sheldon components in normal individuals, positive correlations were established between endomorphy and total cholesterol, cholesterol esters and phospholipids. Negative correlations of similar magnitude were established between ectomorphy and total cholesterol, cholesterol esters and phospholipids. The coefficients of correlation were negligible between mesomorphy and three lipids.

5. When the healthy group of 146 were divided into physique groups (roughly spaced), cholesterol, total cholesterol and phospholipids tended to be highest in endomorphs and lowest in ectomorphs. Cholesterol esters tended to reverse. Comparison of variances showed that the mesomorphs were not only lower than the endomorphs, but tended to have absolutely low variability.

6. The normal data showed that hyperlipemia would be "expected" to be most frequent in endomorphs.

7. When corrected for the difference in physique between the two groups, the difference in the serum lipids between the coronary artery disease patients and the normal individuals did not change the value to any degree, showing that the difference was a real one, not accounted for on the basis of physique alone.

8. Intra-group comparisons in the 97 coro-

nary artery disease patients showed that the general trend of endomorph-ectomorph differences continued, but that the lipid values in coronary mesomorphs were higher than the coronary endomorphs. Hence it was shown that coronary artery disease is characterized not only by mesomorphy, but that coronary mesomorphs differ in their relative lipid levels even within the coronary disease group.

9. The lack of a so-called "critical threshold" of cholesterol, and the maintenance of group differences in the coronary group suggests that here the abnormal metabolism is superimposed on, but does not obscure, the normal pattern.

10. This abnormal pattern seems to express itself most widely and most extensively in the coronary mesomorphs, and is relatively restrained in coronary ectomorphs; it is pointed out that the absolute cholesterol level is not the primary factor, but that differences in diameter of the coronary artery lumen, and the degree of permeability of the coronary artery intima, and predisposition to plaque formation may be equally important.

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Circulatory Dynamics in Spontaneous and Nephrogenic Hypertensive Dogs during the Depressor Response to Acute Inflammation

By J. STAMLER, M.D., A. P. FISHMAN, M.D., L. N. KATZ, M.D., AND S. RODBARD PH.D.

(*with the technical assistance of A. Ellis and F. Williams*)

Cardiac output and blood volume are at control levels in unanesthetized hypertensive dogs during the depressor response to acute inflammation. Hence the fall in blood pressure is due to a decreased total peripheral resistance. The accompanying renal hyperemia indicates that decreased resistance in the renal vascular bed accounts for a significant portion of the fall in total peripheral resistance. Drug studies further suggest that acute inflammation operates to lower blood pressure in hypertensive dogs via mechanisms other than complete paralysis of autonomic vasomotor activity.

AN ACUTE inflammatory process with abscess formation induces a sustained reduction of the blood pressure to normotensive levels in both spontaneous and nephrogenic hypertensive dogs.[1, 2] The mechanism of this prolonged depressor response remains obscure.[3, 4] From hemodynamic considerations, the response may be a result of a marked decrease in either cardiac output or peripheral resistance, or both. Since it is not possible to measure changes in the general peripheral resistance except inferentially, we have undertaken to study the cardiac output in hypertensive dogs during an acute inflammatory reaction with abscess formation. Data were obtained in both anesthetized and unanesthetized hypertensive dogs. Renal blood flow was measured concurrently with the cardiac output to aid in evaluating the relative contributions of the renal and extrarenal systemic vascular beds to any observed reduction of total peripheral resistance. Since alterations in blood volume may influence blood pressure, the circulating blood volume and thiocyanate space were also determined.

In the course of this study, some data on the circulatory dynamics of spontaneous hypertension in the dog[2] were obtained.

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois. The Department is supported in part by the Michael Reese Research Foundation.

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METHODS

Control cardiac output determinations, utilizing the Fick principle,[5] were done on 14 adult healthy male mongrel dogs in the postabsorptive state. Three of these were nephrogenic hypertensive, three were spontaneous hypertensive and eight were normotensive animals. Determinations were done on unanesthetized and on anesthetized animals. The procedure in the unanesthetized dog was based on a modification of Marshall's method.[6, 7]

For the determination in the anesthetized dog, intravenous sodium pentobarbital (25 mg. per Kg.) was administered until surgical anesthesia (stage 3) was achieved. Oxygen consumption was measured using endotracheal intubation. A number 38 or 40 endotracheal catheter with an inflatable cuff was passed into the trachea under direct laryngoscopic visualization. Nupercaine ointment was used to lubricate the catheter and decrease local irritative reflexes. This was supplemented on occasion by local application of 1% cocaine. Following intubation, the cuff was inflated to obstruct the airway around the catheter, thereby confining respiratory exchange to the lumen of the endotracheal catheter. A clinical spirometer connected to the endotracheal tube recorded oxygen consumption and respiratory rate. Mixed venous blood was obtained by passing a number 8 or 9 Cournand catheter into the right heart under fluoroscopic control. A specially constructed split needle[8] was used to obviate ligation and severance of the external jugular vein on passing the catheter. Arterial blood samples were obtained by direct puncture of the femoral artery. Simultaneous arterial and mixed venous blood samples were drawn during oxygen consumption determina-

tions. The blood samples were drawn into heparinized syringes under oil and transferred immediately to chilled test tubes. Duplicate oxygen determinations by the manometric method of Van Slyke and Neill[9] were initiated shortly after blood was drawn.

Intracardiac and systemic blood pressures were recorded with a Hamilton manometer.[10] The criteria for spontaneous and nephrogenic hypertension in the dog have been described previously.[2, 10] A detailed account of the blood pressure data over many months in all the dogs used in this study was presented in previous reports.[2, 3] Renal clearances were done on the unanesthetized and anesthetized postabsorptive animals according to methods previously described.[2] The renal fraction, or per cent of the cardiac output perfusing the kidney, was calculated from the formula

$$\frac{\textit{renal blood flow (cc./min.)} \times 100}{\textit{cardiac output (cc./min.)}}$$

Blood volume and total available fluid were determined on the trained unanesthetized postabsorptive dogs utilizing Evans Blue Dye (T 1824) and sodium thiocyanate respectively, according to modifications of the method of Gregersen and Stewart.[11]

The inflammatory reaction with abscess formation was produced by subcutaneous injection of 2.5 cc. of turpentine in the left axilla; the criteria for a positive depressor response have been previously described.[3]

Total peripheral resistance (TPR), renal vascular resistance (R_R) and extrarenal systemic resistance (E_R) were calculated from the formulas,

$$TPR = \frac{Pm \times 1332}{V_t} \tag{1}$$

$$R_R = \frac{Pm \times 1332}{RBF_t} \tag{2}$$

$$E_R = \frac{Pm \times 1332}{V_t - RBF_t} \tag{3}$$

or

$$\frac{1}{R_{ER}} = \frac{1}{TPR} - \frac{1}{R_R} \tag{4}$$

where Pm = mean blood pressure in mm. Hg, V_t = cardiac output in cc./sec., RBF_t = renal blood flow in cc./sec.[12]

Results

Circulatory Dynamics of Spontaneous and Nephrogenic Hypertension

Unanesthetized Dogs. Data on control cardiac output (C.O.) and cardiac index (C.I.) are presented in table 1. Four unanesthetized normotensive dogs had a mean cardiac index index of 3.9 L/min./M^2; the range was 3.8 to 4.1. These values are in general agreement with those previously reported by other workers.[6, 13, 14, 37] The unanesthetized spontaneous hypertensive dog had a normal mean cardiac index of 2.9 L/min./M^2; the range was 2.7 to 3.1 (table 1). The unanesthetized nephrogenic hypertensive dog also had a normal cardiac index (table 1).[14]

The control renal clearance values and renal fractions of unanesthetized spontaneous hypertensive dogs were in the normal range (table 4).[2] One nephrogenic hypertensive dog (Z36) had clearances at the lower limits of the normal range, the other (Z95) exhibited a definitely reduced renal blood flow and glomerular filtration rate.[2]

All the hypertensive dogs had a normal blood volume and thiocyanate space (table 2).[15, 18, 19] This was true for the spontaneous as well as the nephrogenic hypertensive animals. The mean blood volumes and thiocyanate spaces, respectively, of the normotensive, spontaneous hypertensive and renal hypertensive groups corresponded closely.

Anesthetized dogs. The mean cardiac index for 6 anesthetized normotensive dogs was 3.6 L/min./M^2; the range was 2.5 to 4.6 (table 1). These results agree with those previously reported from this and other laboratories.[14, 16, 17] Compared with values recorded in unanesthetized animals, they have a slightly lower mean and a greater range (table 1). Two anesthetized spontaneous hypertensive dogs had average cardiac index values of 2.8 and 2.9 L/min./M^2, respectively (table 1). These values are all within the normal range; they agree with data obtained on the unanesthetized spontaneous hypertensive dog. It is therefore apparent that the cardiac output is at normal levels in spontaneous hypertension. In accord with previous findings,[14] we recorded normal cardiac output values in anesthetized nephrogenic hypertensive dogs (table 1).

Renal clearances on 1 spontaneous and 2 nephrogenic anesthetized hypertensive dogs prior to abscess induction yielded results agreeing closely with values in unanesthetized ani-

TABLE 1.—*Control Cardiac Output Data*

Dog No.	Weight	S.A.*	No. of determinations	Average A-V O_2 Difference	Cardiac Output Range	Average Cardiac Output	Average Cardiac Index†
Normotensives-Unanesthetized							
	Kg.	M^2		*volumes %*	*L/min.*	*L/min.*	*L/min./M^2*
P1	18.9	.798	2	3.9	3.0–3.4	3.2	4.1
P2	23.4	.915	1	5.9	—	3.6	4.0
P4	14.1	.656	2	3.9	2.4–2.7	2.5	3.8
P5	21.9	.880	2	3.6	3.4–3.8	3.6	4.1
Mean.....	19.6	.815	—	4.3	—	—	3.9
Spontaneous Hypertensives-Unanesthetized							
Z20	32.4	1.131	2	4.9	3.1–3.6	3.3	2.9
Nephrogenic Hypertensives-Unanesthetized							
Z19	15.0	.679	3	4.8	1.8–2.0	1.9	2.8
Normotensives-Anesthetized							
1095	12.3	.588	7	2.7	2.0–3.0	2.4	4.1
Z101	14.0	.652	2	2.2	2.6–3.4	3.0	4.6
Z102	15.2	.684	4	3.4	2.2–2.5	2.3	3.4
P1	18.9	.798	3	4.5	1.8–2.1	2.0	2.5
P2	23.4	.915	2	2.8	2.6–2.7	2.7	2.9
P3	15.8	.707	2	2.5	2.8–2.8	2.8	4.0
Mean.....	16.6	.734	—	3.0	—	—	3.6
Spontaneous Hypertensives-Anesthetized							
Z11	18.8	.796	4	4.2	2.0–2.6	2.3	2.8
Z15	14.5	.668	5	3.7	1.7–2.2	1.9	2.9
Z39	12.6	.610	3	2.9	2.1–2.5	2.2	3.7
Mean.....	15.3	.691	—	3.6	—	—	3.1
Nephrogenic Hypertensives-Anesthetized							
Z36	20.8	.848	6	5.6	1.5–2.0	1.7	2.0
Z95	22.4	.892	4	5.3	1.8–2.9	2.1	2.4
Mean.....	21.6	.870	—	5.5	—	—	2.2

* S.A. = Surface area calculated from the formula S.A. = $\frac{11.2 \times W^{.667}}{10{,}000}$ where S.A. = surface area in square meters, and W = weight in grams.

† Average Cardiac Index = Cardiac output corrected to a surface area of 1 square meter, from the surface area data calculated as indicated above.

mals (table 4). Under anesthesia, dogs Z11 and Z36 had renal fractions within the normal range. Since renal hypertensive dog Z95 had a diminished renal blood flow and normal cardiac output, the renal fraction was reduced (table 4).

Right ventricular, pulmonary arterial and peripheral venous pressures were at normal

levels in both spontaneous and nephrogenic hypertensive dogs.[20, 21, 22]

TABLE 2.—*Control Blood Volume and Thiocyanate Space Data*

Dog No.	No. of Determinations	Blood Volume	Thiocyanate Space
Normotensives			
		cc./Kg.	*cc./Kg.*
1095	2	92	227
Z101	4	94	257
Z102	4	108	255
P1	3	108	359
P2	3	92	297
P3	1	95	331
P4	2	106	332
P5	3	93	302
Z92	1	—	309
Z100	1	63	272
Mean	—	94	294
Lit.*	—	91	294
Spontaneous Hypertensives			
Z11	1	89	276
Z15	5	82	262
Z20	2	74	270
Mean	—	82	269
Nephrogenic Hypertensives			
Z36	3	91	272
Z95	4	83	267
Z93	3	89	302
Z14	4	76	291
Z94	1	—	278
Z81	2	66	263
Z83	2	76	277
Z33	1	—	309
Mean	—	80	282

* Lit. = Review of data in the literature on blood volume and thiocyanate space of dogs determined with T 1824 and thiocyanate respectively, the figures cited above being an average of all data given by D. D. Bonnycastle.[15]

Circulatory Dynamics during the Depressor Response to Acute Inflammation (Abscess)

Unanesthetized dogs. In 2 unanesthetized hypertensive dogs, exhibiting a prolonged depressor response after turpentine injection (Z19, Z20), cardiac output determinations were done on the second, third and fourth day following the turpentine injection. The systolic and diastolic blood pressures fell about 30 mm. Hg to normotensive levels.[3] During this depressor response, the resting cardiac output obtained in the unanesthetized animal did not vary significantly from those obtained during the control period (table 3 and figure 1). Thus, spontaneous hypertensive dog Z20 had a mean control cardiac index of 2.9 L/min./M². During the depressor response to injury, the cardiac index values were 2.4, 3.0 and 3.3 L/min./M² on three successive days. Nephrogenic hypertensive dog Z19 had a mean control cardiac index of 2.8 L/min./M². Following abscess induction, the cardiac index values were 2.6, 2.9 and 2.9 L/min./M² on three successive days (table 3).

In spontaneous hypertensive dog Z20, renal clearances were done on the second day following tissue injury. The blood pressure had fallen from 195/115 to 160/85 mm. Hg. The cardiac output was within the control range (table 3). At this time, renal clearance determinations in the unanesthetized animal revealed a significant renal hyperemia (table 4 and figure 1). The renal fraction increased from 18 per cent before abscess induction to 30 per cent on the second day after turpentine injection. The dog was afebrile at this time.

Renal clearances were done in 3 other unanesthetized hypertensive dogs (Z36, Z95, Z11) during the depressor response to abscess (table 4). In agreement with previous observations,[3] each exhibited an increased renal blood flow, with little change in glomerular filtration rate and a decreased filtration fraction.

Calculation of vascular resistance in dog Z20 revealed a moderate decrease in total peripheral resistance, a marked fall in renal vascular resistance and no significant change in extrarenal systemic resistance (figure 1).

Blood volume and thiocyanate space were determined during the depressor response to abscess in 4 unanesthetized dogs. None exhibited a change in blood volume (table 5). Three showed no alteration in thiocyanate space; one nephrogenic hypertensive dog had a 22 per

TABLE 3.—*Changes in Cardiac Output of Hypertensive Dogs During the Depressor Response to Tissue Injury*

Dog No.	Type Dog	Wt.*	S.A.†	Days after injury	B.P.‡	Heart Rate	Respiratory Rate	Oxygen Consumption	A-V O_2 Difference	Cardiac Output	Cardiac Index
					Unanesthetized Dogs						
		Kg.	*M²*		*mm.Hg*	*per min.*	*per min.*	*cc./min.*	*volumes %*	*L/min.*	*L/min./M²*
Z19	N.H.§	15.0	.679	Control	210/105	96	32	92	4.8	1.9	2.8
				2	190/90	92	20	95	5.4	1.8	2.6
				3	155/85	88	24	100	5.0	2.0	2.9
				4	150/75	84	18	100	5.0	2.0	2.9
Z20	S.H.‖	32.4	1.131	Control	195/115	78	44	162	4.9	3.3	2.9
				2	160/85	88	50	160	6.0	2.7	2.4
				3	145/75	82	54	150	4.4	3.4	3.0
				4	190/90	88	48	180	4.8	3.8	3.3
					Anesthetized Dogs						
Z36	N.H.	20.8	.848	Control	190/120	144	11	96	5.6	1.7	2.0
				4	135/80	164	20	83	1.4	5.9	7.0
Z95	N.H.	22.4	.892	Control	190/115	158	18	113	5.3	2.1	2.4
				4	150/80	150	6	89	2.5	3.6	4.0
Z11	S.H.	18.8	.796	Control	190/110	139	14	95	4.2	2.3	2.8
				3	120/75	142	34	110	1.8	6.1	7.7

* Wt. = weight in kilograms.
† S.A. = surface area, see table 1 for formula used in calculation.
‡ B.P. = blood pressure in millimeters of mercury.
§ N.H. = nephrogenic hypertensive.
‖ S.H. = spontaneous hypertensive.

TABLE 4.—*Renal Clearance and Cardiac Output Data in Unanesthetized vs. Anesthetized Hypertensive Dogs during the Depressor Response to Acute Inflammation*

Dog No. and Type	Days After Injury	Unanesthetized							Anesthesized						
		B.P.	GFR	RPF	RBF	FF	C.O.	Renal Fraction*	B.P.	GFR	RPF	RBF	FF	C.O.	Renal Fraction
		mm.Hg	*cc./min.*	*cc./min.*	*cc./min.*	*%*	*L/min.*	*%*	*mm.Hg*	*cc./min.*	*cc./min.*	*cc./min.*	*%*	*L/min.*	*%*
Z20	Control	195/115	113	332	604	34.0	3.3	18	—	—	—	—	—	—	—
S.H.	2†	160/85	118	407	798	29.0	2.7	30	—	—	—	—	—	—	—
Z36	Control	190/120	58	179	326	32.4	—	—	—	53	183	327	29.0	1.7	19
N.H.	4†	135/80	63	248	427	25.4	—	—	160/85‡	39	91	157	42.9	5.9	3
Z95	Control	190/115	58	141	266	41.1	—	—	170/125‡	69	145	274	47.6	2.1	13
N.H.	4†	150/80	80	247	426	32.5	—	—	140/100§	63	105	181	60.0	3.6	8
Z11	Control	190/110	65	192	337	33.9	—	—	150/115§	71	199	349	35.7	2.3	15
S.H.	3‖	120/75	72	242	391	29.8	—	—	150/75¶	42	98	144	42.9	6.1	2

Note: B.P. = blood pressure; GFR = glomerular filtration rate; RPF = renal plasma flow; RBF = renal blood flow; FF = filtration fraction; C.O. = cardiac output; S.H. = spontaneous hypertensive; N.H. = nephrogenic hypertensive.

* Renal Fraction RBF/C.O. † Dog was afebrile at this time. ‡ Under anesthesia for 90 minutes at time of B.P. recording. § Under anesthesia for 220 minutes at time of B.P. recording. ‖ Febrile, temperature elevated 1.8 C. above control level. ¶ Under anesthesia for 180 min. at time of B.P. recording.

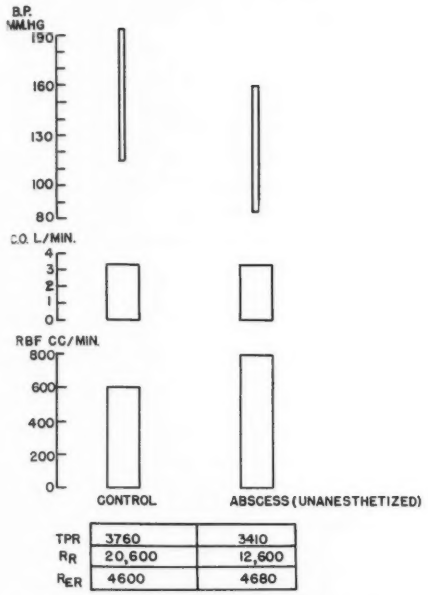


FIG. 1. Cardiorenal dynamics during acute inflammation with abscess formation in unanesthetized hypertensive dog Z20. All data, both control and experimental, were obtained in the unanesthetized animal. The blood pressure fell from hypertensive to normotensive levels thirty-six hours after subcutaneous injection with turpentine. The depressor response persisted for two and one-half weeks. Top and bottom of the columns in the upper graph represent systolic and diastolic blood pressure respectively (B.P. in mm. Hg). The control represents mean values recorded over many months. The data during abscess are mean pressures during the second through the fourth day of the depressor response. The control cardiac output value (C.O. L/min., height of column, middle graph) is an average of several determinations. Cardiac output data during abscess are an average of 3 determinations (see table 4). The control renal blood flow (RBF cc./min., height of column, lower graph) is an average of several determinations. The data during abscess were obtained on the second day after turpentine injection. Values for vascular resistances (bottom table) are calculated from data in table 5. *TPR* is total peripheral resistance in absolute units (a.u.); R_R is the renal vascular resistance in a.u.; R_{ER} is the extrarenal systemic resistance in a.u.[12] Discussed in text.

cent reduction in total available fluid on the fifth day after abscess induction (table 5). This last value (227 cc./Kg.) is within the low range of normal for this determination in the dog.[15]

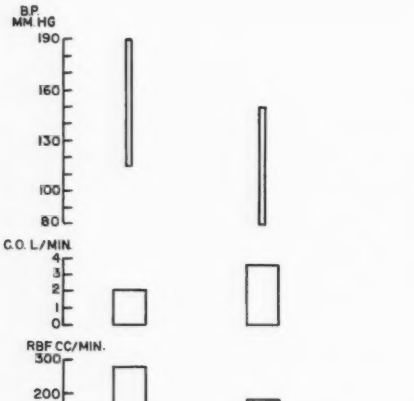
Anesthetized dogs. During the depressor response to tissue injury, cardiac output determinations during anesthesia with sodium pentobarbital were done on dogs Z36, Z95 and Z11. Under these circumstances, the cardiac output was in each case considerably above the control value (table 3 and figure 2). The increases in cardiac output were 245, 67 and 170 per cent respectively.

TABLE 5.—*Changes in Blood Volume and Thiocyanate Space of Hypertensive Dogs during Depressor Response to Acute Inflammation.*

Dog No.	Type Dog	Days After Injury	Blood Volume	Thiocyanate Space
			cc./Kg.	*cc./Kg.*
Z93	N.H.*	Control	88.6	302
		5	86.8	320
		9	93.4	304
Z14	N.H.	Control	76.3	291
		5	69.0	227
Z36	N.H.	Control	90.5	272
		9	80.5	301
Z15	S.H.†	Control	81.8	262
		2	84.3	—
		9	93.8	289

* N.H. = nephrogenic hypertensive.
† S.H. = spontaneous hypertensive.

In these anesthetized dogs, renal clearances were done immediately following the cardiac output determination. Each exhibited a marked depression of renal blood flow, with slight to moderate decrease in glomerular filtration rate and an increased filtration fraction (table 4 and figure 2). This renal ischemia in these anesthetized dogs during the depressor response to tissue injury was in marked contrast to the renal hyperemia these same animals exhibited earlier on the same day in clearances done prior to anesthesia (table 4). Calculation of the renal fraction for these anesthetized dogs revealed a marked depression, in contrast to the considerable rise exhibited by unanesthetized dog Z20 (table 4). Calculation of vascular resistance revealed a marked fall in total peripheral resistance, a considerable rise in renal



TPR	5480	2710
R_R	43,800	53,300
R_{ER}	6260	2860

FIG. 2. Cardiorenal dynamics during acute inflammation with abscess formation in anesthetized hypertensive dog Z95. The blood pressure fell from hypertensive to normotensive levels twenty-four hours after subcutaneous injection with turpentine. The depressor response persisted for two weeks. Top and bottom of the columns in the upper graph represent systolic and diastolic blood pressure respectively (B.P. in mm. Hg). Both control and experimental values were recorded in the anesthetized dog. Surgical anesthesia had no significant effect on diastolic or systolic blood pressure during either the control or experimental periods. All the experimental findings in the anesthetized animal (blood pressure, cardiac output, renal blood flow) were obtained on the fourth day after turpentine injection (see table 5). The control cardiac output value (C.O. L/min., height of column, middle graph) is an average of several determinations (see table 1). The control renal blood flow (RBF cc./min., height of column, lower graph) is an average of several determinations. The renal blood flow under anesthesia during the depressor response to abscess was markedly depressed, although a renal hyperemia was recorded earlier on the same day in an unanesthetized study (see table 5). Values for vascular resistances (bottom table) are calculated from data in table 5. For other symbols see figure 1. Discussed in text.

vascular resistance and a marked decrease in extrarenal systemic resistance (figure 2).

DISCUSSION

Spontaneous hypertension in the dog[2] is hemodynamically similar to experimental nephrogenic and human essential hypertension, since all three exhibit normal cardiac output, circulating blood volume, thiocyanate space, venous pressure and pulmonary arterial pressure.[14, 18–22] The elevated systemic arterial pressure seen in canine spontaneous hypertension must therefore be attributed (as in experimental nephrogenic and human essential hypertension) to an increased peripheral resistance.*

In previous studies[1, 3] it was postulated that this increased peripheral resistance is reversible, since these hypertensive dogs respond to acute inflammation with a fall in blood pressure[1] and a renal hyperemia.[3] The present study reveals that during this inflammatory-depressor reaction, no alteration occurs in the cardiac output, blood volume or thiocyanate space of unanesthetized hypertensive dogs. Therefore, abscess induction, in some undetermined way, effects a decrease in total peripheral resistance; this is responsible for the blood pressure fall. This finding verifies the concept that in hypertensive disease the systemic arteriolar hypertonus is reversible.[3, 18, 20, 22]

Renal hyperemia, in the presence of a normal cardiac output and a fall in blood pressure indicates a markedly reduced over-all renal resistance to blood flow.[23, 24] Since the renal fraction is increased, the decrease in renal vascular resistance is out of proportion to any decrease in resistance in the extrarenal systemic vascular bed. It is not possible to determine precisely whether the decrement in renal vascular resistance alone is adequate to account for the entire depressor response.

Prior to the induction of an acute inflammatory reaction, cardiac output and renal clearance values for animals under anesthesia correspond closely with findings in unanesthetized dogs. Following abscess induction, these values in anesthetized animals are markedly different from those in unanesthetized dogs. The unanesthetized hypertensive dog exhibits a renal hyperemia and unchanged cardiac output dur-

* We have previously discussed the possible pathogenetic relationship between this increase in peripheral resistance and the somewhat different patterns of renal physiology and morphology in these three types of hypertension.[2]

ing the sustained depressor response to inflammation. The anesthetized animal exhibits a marked renal ischemia and an elevated cardiac output. Thus, neither the induction of an inflammatory process alone, nor the exhibition of pentobarbital anesthesia alone, elicits a cardiac output change. However, the combination of these two factors drastically alters circulatory dynamics; a marked increase in cardiac output ensues. This augmented cardiac output is apparently secondary to a marked acute fall in total peripheral resistance brought about by the combination of the two stressful conditions.[25, 26] Apparently abscess (chronic effect) and pentobarbital (acute effect) together severely depress peripheral resistance.[27–29] As resistance to flow decreases, cardiac output increases. This readjustment is accomplished without any recorded deviation in right atrial pressure.[26]* Concurrently the renal blood flow and renal fraction decrease markedly. As the extrarenal systemic resistance falls precipitously, the renal vascular resistance rises sharply. The renal vasoconstriction†, together with the increased cardiac output, serves to maintain blood pressure.‡ These compensatory responses of the circulation are brought about via regulatory mechanisms at present poorly understood. Epinephrine release may be at least partly responsible for the observed cardiorenal dynamic pattern.

Bradley and co-workers[36] have studied cardiorenal circulatory dynamics in unanesthetized normotensive and hypertensive patients* during an acute afebrile depressor response to pyrogens. Under these somewhat different conditions, the cardiac output and the renal blood flow are both markedly increased. The observed fall in blood pressure is undoubtedly due to a marked reduction in total peripheral resistance, which has a large component in the renal pathway. During the more chronic depressor response to abscess in unanesthetized hypertensive dogs, no such increase in cardiac output occurs. Only when blood pressure homeostasis is placed doubly in jeopardy by the combined insult of inflammation and pentobarbital anesthesia does such an increase in cardiac output result. Under the latter conditions, we observed a decrease in renal blood flow rather than an increase as in Bradley's experiments. It would appear therefore that the mechanisms involved in Bradley's patients and our dogs are not identical.

The mechanism of the reduction in total peripheral resistance during the depressor response to abscess is not apparent. Among the several possibilities previously discussed[3] and now under investigation in this laboratory, consideration must be given to the role of the nervous system. Barbiturates in anesthetic doses tend to depress the vasomotor apparatus and produce vasodilatation via both a central and peripheral action.[27–29] These pharmacologic actions of pentobarbital apparently effect a marked additional decrease in total peripheral resistance in hypertensive dogs undergoing a depressor response to inflammation.† This further fall in peripheral resistance superimposed by barbiturates presupposes a considerable degree of residual neurogenic vasomotor activity

* Stead and co-workers[25] have postulated that in the presence of an adequate amount of blood, this compensatory response of the cardiac output to an acute fall in peripheral resistance is brought about by active changes in cardiac relaxation and contraction, probably mediated via reflex (not humoral) pathways.

† An alternate possibility must be considered, namely that effective renal blood flow is reduced under these circumstances because of the operation of a renal shunt mechanism.[30] In this case, the para-aminohippurate clearance would not be a measure of true renal blood flow; our calculation of renal resistance would not be valid. Such a renal shunt would greatly decrease renal resistance, and would thus contribute to the generalized fall in peripheral resistance. The kidney would not serve as a buffer protecting against shock.[31, 32] In view of recent work, [33, 34] however, it is unlikely that such a shunt mechanism plays a significant role in man or in the dog.

‡ It is possible that some other areas of the systemic circuit (e.g., the skin) may also respond with vasoconstriction, but the total effect is a decreased peripheral resistance.

* Normotensive and hypertensive subjects respond in a qualitatively similar manner. We have found that normotensive dogs exhibit a depressor response to abscess qualitatively similar to that of hypertensive animals.[35]

† The autonomic blocking agent tetraethylammonium chloride similarly elicits a further blood pressure fall in such dogs.[35]

in unanesthetized hypertensive dogs during the depressor response to inflammation; at least some autonomic activity must continue during the sustained depressor response to abscess. Therefore, the inflammatory reaction operates to lower blood pressure without completely paralyzing autonomic control of blood vessels. It remains to be elucidated whether or not the depressor response is due to partial block (depression without paralysis) of neurogenic vasomotor activity.

Summary

1. The cardiodynamic pattern of spontaneous hypertension in the dog is essentially similar to that of canine nephrogenic and human essential hypertension. In all three, a dynamic increase in total peripheral resistance prevails which is potentially reversible.

2. The cardiac output and blood volume remain unchanged in unanesthetized spontaneous and nephrogenic hypertensive dogs during the fall in blood pressure which occurs during an acute inflammatory process with abscess formation. The sustained fall in blood pressure is therefore due to a decrease in the total peripheral resistance.

3. During the depressor response to abscess in the unanesthetized hypertensive dog, a renal hyperemia with increased renal fraction occurs which may account for a significant portion of the decrease in total peripheral resistance.

4. The anesthetized (pentobarbital) hypertensive dog responds differently during the depressor response to inflammation. In this animal, an increased cardiac output is seen. Concomitantly, the renal blood flow is markedly reduced. The fact that pentobarbital anesthesia superimposed on abscess results in a marked increase in cardiac output with no further change in blood pressure shows that the total peripheral resistance is further reduced. The kidney does not participate in this reduction in resistance. Instead a marked renal ischemia occurs, perhaps as a compensatory response operating to maintain the total peripheral resistance. This, together with the increased cardiac output, serves to prevent a marked fall in blood pressure.

5. The ability of pentobarbital anesthesia further to reduce total peripheral resistance during the depressor response to inflammation suggests that abscess operates to lower blood pressure in hypertensive dogs without completely paralyzing autonomic vasomotor activity.

Acknowledgments

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The Effect of Exercise on the Plasma Volume of Patients with Heart Failure

By ROBERT P. GILBERT, M.D., AND J. K. LEWIS, M.D.

Exercise performed in the supine position by patients with congestive failure was found to cause not only a greater elevation of the peripheral venous pressure than it causes in normal persons, but also a proportionately greater fall of the plasma volume.

IT IS NOW generally accepted that in heart failure of all types the cardiac output is reduced relative to the needs of the body at that time.[1–3] Beyond this however, disagreement and uncertainty still confound our ideas of the causal interrelationships between this mechanical incompetence of the heart and the phenomena of clinical heart failure. Thus, the elevation of the venous pressure is regarded by some as related directly to the decrease in cardiac output and as the primary or initiating cause of edema.[4–6] By other workers[7–9] it is viewed as a purely static manifestation produced by the increase of the extracellular fluid volume or at times by changes in venous tone. In this regard though, it is worth recalling that many observers[10, 11] have noted that exercise produces an abnormally great rise of the peripheral venous pressure in persons with cardiac failure even though the peripheral venous pressure at rest may have been normal. This has recently been confirmed by Felsovanyi and Lewis[12] and by others.[13, 14] By increasing the body's demands beyond the capabilities of a heart barely "compensated" at rest, exercise renders latent heart failure obvious. Landis, Brown, Fauteux and Wise[4] have gone into this problem, using dogs. They ligated a coronary artery or induced auricular fibrillation to simulate clinical myocardial incompetence. They then found that exercise caused the central venous pressure to rise, though it had not risen during similar exercise beforehand. They were led to propose an hypothesis to account for the sequence of events in developing heart failure which may be paraphrased as follows:

Impaired myocardial competence. ——→ Inability of the heart to cope with the venous return when this exceeds the heart's competence. This is intermittent at first. ——→ Repeated and intermittent pooling of the blood on the venous side with a rise in the venous pressure. ——→ Loss of fluid into the extravascular spaces. ——→ The loss of fluid and the venous pooling constitute a fall in the circulating blood volume, intermittent at first. ——→ Compensatory changes to increase the extracellular fluid volume and the blood volume. (a). Vasoconstriction, which, as it affects the kidneys, is responsible in part for the retention of water and electrolytes. (b). Vasoconstriction of vessels leading to the bone marrow with stimulation of erythropoiesis. ——→ Further increase of venous pressure due to plethora.

The matter to be presented concerns only one step in this chain of events: the increased venous pressure consequent upon exercise in patients with cardiac failure does indeed lead to a greater fall of the plasma volume than occurs in normal subjects who show little or no rise in venous pressure.

Previous workers have studied the changes in the blood volume during exercise, and in general it has been found to fall.[15–18] In the present study the amount of exercise was insufficient to produce an appreciable drop of the plasma volume in normal individuals.

METHODS

The subjects studied were patients from either the medical ward or the outpatient clinic. Control studies were done on patients with no evidence of right-sided heart failure. With few exceptions the tests were performed in the morning in the post-absorptive state, and always after at least forty-five minutes rest in the horizontal position.

The exercise was performed while supine, and consisted of repeatedly pushing a foot board to raise a weight along a given arc as described by Felsovanyi and Lewis.[13] Each stroke required the ex-

From the Department of Medicine, Stanford University School of Medicine, San Francisco, Calif.

penditure of about 28 foot-pounds of work, and the usual rate was 30 to 50 strokes per minute. For patients who were made uncomfortable, the slower rate was used. When more than one test was performed by the same person, approximately the same rate was used each time. Exercise was continued for fifteen minutes except for a few instances of fairly pronounced failure.

Oiled 20 ml. syringes with 18-gage needles were used to take samples from an arm vein before and just at the conclusion of the exercise period. Every effort was made to avoid stasis. It was found to be unwise to draw blood from the three-way stopcock of the venous pressure manometer, as slight dilution by the sodium citrate solution was hard to avoid. Five ml. of blood were placed in a commercially prepared tube containing ammonium and potassium oxalate as anticoagulants. The remainder was allowed to clot in a paraffined centrifuge tube. The separated serum was centrifuged a second time.

Hematocrits were determined in duplicate or triplicate with Wintrobe tubes.

Serum protein levels were measured with the gradient tube of Lowry and Hunter.[19] Results were found to check at least to within 0.10 Gm. per 100 cc., though the absolute accuracy was probably less.

For measuring the venous pressure in the antecubital vein an ordinary water manometer containing 2.5 per cent sodium citrate was used. By flushing out the needle and tubing from a reservoir it was possible to observe the pressure for an indefinite period. Pressures were measured from the phlebostatic level of Winsor and Burch.[20]

The plasma volume was determined with the dye T-1824, following in general the technic described by Hopper, Tabor and Winkler[21] except that the Coleman spectrophotometer was used.

Alterations in plasma volume were measured in three ways. In some cases the long indirect method of Gibson and Evans[22] was used. In view of the demonstration by Ebert and Stead[23] that exercise caused the optical density of the serum itself to increase, control determinations were made the day before to find out in each case to what extent the exercise employed would alter the optical density of the serum. In general this correction was found to be insignificant (change in optical density of less than .005). Kaltreider[24] found that exhausting exercise was necessary to produce the effect.

Changes in the plasma volume were also calculated from the changes in the serum protein concentration and from changes in the venous hematocrit by substituting in the relationships:

$$\textit{Total circulating protein} = \textit{protein concentration} \times \textit{plasma volume}$$

$$\textit{RBC volume} = \textit{hematocrit} \times \textit{blood volume}$$

Following exercise the total circulating protein and the red blood cell volume were assumed to have remained constant. The new plasma volume and the new blood volume were the only unknowns. The change in blood volume was assumed to equal the change in plasma volume.

It is realized that these technics are not proof from error. Arterial blood sampling would have eliminated the possibility of error due to local stasis. Increased loss of protein through the capillary membrane at higher venous pressures[25] may have caused falsely low values for the plasma volume decrement calculated by both the long indirect dye method and the change in serum protein method. The red cell volume is overestimated by using the venous or arterial hematocrit, which have been shown to be higher that the true body hematocrit.[26] This would cause the values for the plasma volume changes as calculated from the alterations in hematocrit to be higher than the true change. It was assumed that erythrocytes were neither added to nor lost from the circulation. Nylin[27] was unable to show any addition to the total red cell volume on exercise. Any trapping of cells but not of plasma would lead to a decrease in hematocrit and yield falsely low values for the plasma change. The initial value obtained for the plasma volume was doubtless too high because of the poorly understood extravascular loss of dye.[28, 29] Some of the errors were obviated by expressing the change as a per cent of the initial volume. This also made it possible to compare changes in different individuals and in the same individual after alterations of the resting plasma volume.

Results

The results are summarized in table 1. Peripheral venous pressure readings before exercise were averaged to obtain a figure for the resting venous pressure. For the exercise period the venous pressures at the end of each minute were averaged to obtain the mean level. In a few instances it was necessary to interpolate on a graph to obtain readings at the proper time intervals. The difference between the resting venous pressure and the mean level during exercise was taken as the venous pressure increment. The determinations are arranged according to the order of the resting venous pressures. With normal resting venous pressures, and viewing both tables together, it is seen that exercise may or may not produce a rise in the venous pressures. When the resting venous pressure is above the usual normal limit of 150 mm., a further rise on exercise seems quite likely to occur. An average value was also derived for the per cent change of

TABLE 1.—*Effect of Exercise on Venous Pressure and Plasma Volume*

Case	Diagnoses	Plasma Volume	Resting V.P.	V.P. on Exercise		Percent Fall of Plasma Vol.			
				Max.	Mean Increment	Mean	By Serum Protein	By Hematocrit	By Dye Curve
Group I: Subjects Without Heart Failure									
		ml./Kg.	*mm. sodium citrate*	*mm. sodium citrate*	*mm. sodium citrate*				
3	No disease	45	89	120	21	0.8	0.0	0.0	2.3
6	Dermatitis	43	94	155	17	0.8	1.5	—	0.0
3	No disease	45	99	98	−5	0.0	0.0	—	—
7	? Control. S.B.E. under treatment. Apparently compensated	51	105	148	34	0.7	0.0	0.6	1.6
8	Polycythemia vera	42	112	125	7	0.0	0.0	0.0	—
9	No disease	58	114	137	3	0.0	—	0.0	0.0
7	? Control. S.B.E. under treatment. Apparently compensated	51	117	163	33	0.5	0.5	—	—
10	? Control. Hypertension. Apparently compensated.	45	127	160	13	0.9	1.8	0.0	—
10*	Same	45	150	170	16	1.2	1.2	—	—
Averages		47	112	142	15	0.5	0.6	0.1	1.0
Group II: Subjects with Heart Failure									
1A†	R.H.D. with M.S., M.I. and A.S.	—	42	72	18	3.3	2.5	4.0	—
2	A.S.H.D.	—	81	148	51	2.9	2.9	—	—
4	A.S.H.D.	63	89	173	75	1.5	2.0	0.0	2.3
5	A.S.H.D.	—	93	134	30	4.4	2.5	6.3	—
1B‡	R.H.D. with M.S., M.I. and A.S.	64	93	173	65	3.7	5.1	2.3	—
5	A.S.H.D.	46	98	193	77	5.4	5.4	—	5.4
5	A.S.H.D.	46	106	240	98	5.1	5.1	—	—
5	A.S.H.D.	—	119	168	40	2.9	3.6	2.1	—
5	A.S.H.D.	47	134	154	17	1.9	1.9	1.9	—
1C§	R.H.D. with M.S., M.I. and A.S.	70	145	213	51	5.6	5.1	4.2	7.4
4	A.S.H.D.	52	168	183	15	5.4	4.8	6.0	—
11	Thyrotoxicosis, congestive failure	53	203	278	59	5.6	5.3	5.8	—
12	A.S.H.D. Hypertension	—	204	372	109	8.2	6.9	9.6	—
1D	R.H.D. with M.S., M.I. and A.S.	45	213	292	68	5.3	4.4	6.1	—
1E‖	Same	70	220	337	104	11.2	10.4	12.0	—
1D	Same	65	246	335	73	5.9	6.3	5.4	—
Averages		56	141	217	59	4.9	4.6	5.0	5.0

* Case 10 undergoing forced water diuresis. † Case 1 after diuresis and ouabain. ‡ Case 1 after diuresis, but five days after ouabain. § Case 1 before diuresis, but after ouabain and one test after test 1E. ‖ Case 1 before any treatment.

Experiments are arranged in the order of the resting venous pressure prior to the commencement of exercise. As this varied depending upon the current status of the patient the tests for one subject are scattered throughout the table.

Key to Abbreviations: A.S.H.D., arteriosclerotic heart disease; R.H.D., rheumatic heart disease; S.B.E., subacute bacterial endocarditis; M.S., mitral stenosis; M.I., mitral insufficiency; A.S., aortic stenosis.

the plasma volume as determined by one or more of the three methods.

It is evident on inspection that the venous pressure was found to rise more in subjects with heart failure. Similarly the values for the plasma volume fall were all higher in the heart failure group. Few successive determinations were performed on subjects in a steady state, so that the spread on successive determinations cannot be determined as an index of the error of the methods. If, however, the plasma volume fall in normal subjects is assumed to be actually zero, then a plasma volume fall of 1.2 per cent or greater should be significant, as this was the highest value found. For the patients with heart failure the plasma volume fall was found to be consistently larger than 1.2 per cent (smallest value 1.5). A distinct correlation between the venous pressure increment and the plasma volume fall can be shown when these two functions are plotted against each other as in figure 1. The method of least mean squares was used to obtain the relationship indicated by the line on the graph. The correlation coefficient was .79. That the precision of the results obtained is not to be regarded as absolute may be inferred from the intercept on the ordinate which would indicate a plasma volume fall of 0.3 per cent with no change in the venous pressure. The values for case 4, which are circled on figure 1, are thought to be in error due to dilution from the manometer in the first instance and to stasis in the second.

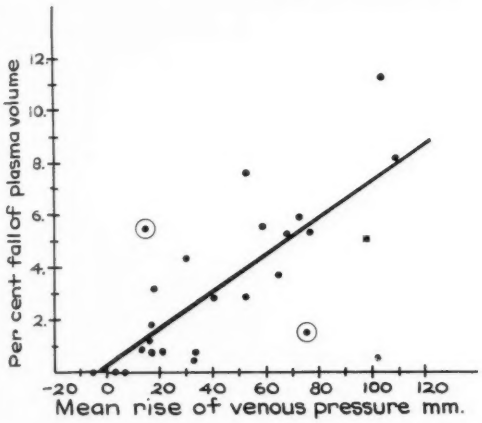

FIG. 1. The Per Cent Fall of the Plasma Volume as Related to the Mean Venous Pressure Increment during Exercise for Fifteen Minutes. The equation $y = 0.32 - 0.069x$ was obtained by the method of least mean squares, letting y equal the per cent fall of the plasma volume and x the mean venous pressure increment in millimeters of citrate solution. This equation is represented by the straight line. The values for the per cent fall of the plasma volume are the average of the results obtained by one or more of the three methods mentioned in the text. The correlation coefficient is .79.

TABLE 2.—*Effect of Exercise on the Venous Pressure and Plasma Volume before and after the Administration of Digitoxin or Ouabain.*

Case	Drug and Dosage	Interval From Test Before	Venous Pressure Increment		Percent Fall of Plasma Volume	
			Before	After	Before	After
		days				
4*	Digitoxin 1.2 mg.	1	75	15	1.5	5.4
5	Ouabain 0.5 mg., digitoxin 0.6 mg., then 0.1 mg. daily	14	77	30	5.4	4.4
5	Digitoxin increased to 0.2 mg. daily	7	30	17	4.4	1.9
10	Digitoxin 1.2 mg. (control)	1	13	16	0.9	1.2
1	Ouabain 0.5 mg. just prior to second test	1	104	51	11.2	5.6
1†	Ouabain 0.5 mg. just prior to second test	8	73	68	5.9	5.3

* Plasma volume fall figures thought to be in error for technical reasons.

† Undergoing forced water diuresis.

The slope of the line in figure 1, .069, defines the average percent fall of the plasma volume per millimeter rise of the peripheral venous pressure over a period of fifteen minutes. For any given case the milliliters of fluid lost from the vascular tree over fifteen minutes should then be the product of the slope times the venous pressure rise in millimeters, times the plasma volume in milliliters, divided by 100. If one should assume a venous pressure rise of 50 mm. of water for fifteen minutes in a subject with a plasma volume of 3000 ml., this would be: $\frac{.069 \times 50 \times 3000}{100}$ or

103 ml. For a 70 Kg. subject (plasma volume of 43 ml./Kg.) this would be $\frac{103}{15 \times 5 \text{ cm.} \times 700}$ or 0.00196 ml. of fluid lost per centimeter rise of the venous pressure per minute per 100 *grams* of tissue. This figure can be compared with the values obtained by Landis and coworkers, one of the highest of which was 0.0033 ml. per minute per centimeter rise of venous pressure per 100 *milliliters* of tissue.[30] The discrepancy is not of alarming size.

In six of the experiments included in table 1 the response to exercise was studied before and after the administration of digitoxin or ouabain. The results are shown in table 2. As indicated above the results in case 4 are thought to be in error due to technical reasons. In most instances there appears to have been a definite lessening of the venous pressure increment, and concomitantly of the loss of plasma volume. Previous studies[12] have shown that digitoxin produces a fairly constant reduction or abolition of the venous pressure rise during exercise in patients with cardiac failure.

Discussion

The data just cited demonstrate once more the occurrence of an abnormal elevation of the venous pressure on exercise in subjects with congestive failure. This elevation may be manifested though the resting venous pressure is normal. As suggested nearly forty years ago[31] the obvious explanation for this observation would be an inability of the heart to increase its output. It has recently been shown that in persons with cardiac insufficiency the output fails to rise during exercise as it does in normal subjects.[32] Furthermore, this venous pressure rise on exercise can be reduced or abolished by the digitalis glycosides which are known to raise the output of the failing heart. If it is conceded that exercise must cause the venous return to increase at once, and if the heart is unable to transfer this added blood to the arterial side, the accumulating fluid must necessarily elevate the pressure within the veins, unless there is a decrease in venous tone. The accumulated blood necessary to sustain a rise in the venous pressure could be drawn not only from portions of the systemic circuit but from the pulmonary circulation as well. Fenn and others[33] have shown that pressure breathing can displace upwards of 500 ml. of blood from the lungs. A similar rise of the venous pressure in subjects with cardiac failure can be produced by passive leg raising or by pressure on the abdomen. In these instances there is an obvious increase of the venous return to an extent that the failing heart is unable to handle it. This rise can occur with a normal or low total blood volume[34] and so cannot be due to an increased blood volume filling out the vascular system as a whole. It does not occur in normal subjects as might be expected if sudden venous constriction were the cause.

The data presented in the table seem to justify the conclusion that the abnormal rise of the venous pressure is accompanied by a loss of fluid from the vascular tree. Indeed some degree of proportionality is evident in figure 1. From past experiences with the effects of an increased venous pressure one could safely predict this finding.[4, 30, 35-37] In the present instance, an acute rise of the venous pressure has apparently initiated the formation of edema.

The increased venous pressure and decreased plasma volume brought about by exercise in patients with congestive failure can be viewed as a change for the worse in the balance between the ability of the heart as a pump and the demands placed upon it. Probably a similar change occurs in acute heart failure as seen clinically, except that in this instance it results from a sudden decrease in the heart's ability as a pump rather than from a sudden increase in the demands placed upon it.

To what extent these acute factors are operative in chronic heart failure is uncertain. Certainly in its early stages the repeated, if transitory, rises in the venous pressure and associated falls in the plasma volume consequent upon increased activity would be expected to initiate a compensatory retention of fluid as pointed out by Landis and others.[4] Furthermore, Blake and Bradley[38] have shown that elevation of the renal venous pressure alone

may lead to decreased renal excretion of salt and water. Further discussion of the relationships between plasma volume, venous pressure and renal function is beyond the scope of this paper, and has been well covered in several recent reviews.[39]

SUMMARY

1. The effects of exercise on the peripheral venous pressure and plasma volume were studied in normal subjects and in patients with congestive failure.

2. In accordance with previous work by others, exercise was found to produce a conspicuous rise of the peripheral venous pressure of patients with heart failure.

3. This transitory rise of the peripheral venous pressure was accompanied by a roughly proportionate decrease of the plasma volume.

4. It is felt that this rise in peripheral venous pressure is due to inability of the heart to sufficiently increase its output, and that the resultant fall in plasma volume may be at least partly responsible for the renal retention of water and salt.

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Antidiuretic Action of the Urine of Patients in Cardiac Failure

By BERNARD A. BERCU, M.D., STANLEY N. ROKAW, M.D., AND EDWARD MASSIE, M.D.

Stimulated by the increasing interest in the operation of antidiuretic principles and the recent development of new concepts of the mechanism of heart failure, this investigation was planned to study antidiuretic effects of the urine of patients with heart failure. It is noteworthy that an antidiuretic effect was induced in hydrated dogs by the intravenous injection of concentrated dialyzed urine of 12 of 15 patients with congestive heart failure. No such effect was exerted by urine from normal controls. Additional studies indicated that the antidiuresis could not be attributed to a substance with the characteristics of commercial Pitressin.

INCREASING interest in the operation of antidiuretic principles in the normal and diseased organism has been stimulated by the recent writings of various investigators. Verney[1] studied the production of acute antidiuresis in animals by noxious stimuli and by hypertonic intracarotid injections. He showed that liberation of posterior pituitary antidiuretic hormone is determined by the osmotic pressure of the arterial plasma. Robinson and Farr[2] investigated the antidiuretic effects of urine from patients with acute nephritis, the nephrotic syndrome, and Cushing's syndrome, as well as other conditions. By using the rat assay method of Burn,[3,4] they found an antidiuretic substance in the urine of these patients and correlated this with the presence of clinical edema. Ralli and co-workers[3] found the presence of such a urinary factor in patients with cirrhosis, and Teel and Reid[4] concerned themselves with its occurrence in eclampsia and pre-eclampsia. Others[20,21] studied the finding of antidiuretic principles in the urine in acute hepatitis. Since the conventional explanation for the mechanism of cardiac failure has been challenged by many workers,[5–7] the important report of Warren and Stead[8] concerning their finding of diminution of renal flow and salt clearance in this condition inevitably produced widespread interest in and stimulated further investigation of all the possible etiologic factors. The concept of the kidney as a "key organ" in initiating the chain of events leading to the manifestations of cardiac failure is most intriguing, but the complexities governing water balance have to some extent interfered with adequate evaluation of this concept. It was thought important therefore, to investigate the presence of antidiuretic principles in the urine of normal individuals and of patients with congestive heart failure.

From the Departments of Internal Medicine and Physiology, Washington University School of Medicine and the Heart Station, Barnes Hospital, St. Louis, Mo.

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PROCEDURE

Two normal mature female dogs weighing 15.8 Kg. and 12.2 Kg., respectively, were maintained in metabolism cages on daily horsemeat (2 pounds each), Purina chow, and water ad libitum. Perineotomy had been performed and healed before the experimental period to enable access to the urethra for indwelling catheters. The dogs were trained to spend long periods suspended in a canvas sling and evidenced no emotional disturbance at the procedures of hydration, intravenous injection, or catheter manipulation. The dogs were hydrated at the start of each experiment with tap water (35 cc. per Kg. of body weight introduced by stomach tube). The resultant urine output was collected directly into volumetric containers and measured at approximately four minute intervals. In preliminary experiments, in attempting to secure prolonged high level urine flows (3 to 4 cc. per minute), we had learned that a lag of thirty to fifty minutes might be expected between the time of ingestion of a given drink and the time of appearance of a diuresis increase, and that a falling off in the rate of flow from peak values after a single hydrating drink began between ninety and one hundred twenty minutes after ingestion. In addition it was found that smaller added drinks (1½ per cent of body weight), spaced in

accordance with these observations, provided sustained diuresis at desired levels without causing regurgitation by the animals. When needed, such subsequent drinks of tap water were administered directly to the dogs without disturbance or removal from the sling.

Commercial Pitressin* (20 pressor units per cc.) was used as the bio-assay standard. This was freshly prepared during each experiment by dilution with physiologic (0.9%) saline to a concentration of 0.2 milliunits per cc. Intravenous administration of this substance produced antidiuretic effects in direct proportion to the dose given. Doses of 0.05 to 0.1 milliunits were sufficient to produce a significant drop in urine output when given to dogs in water diuresis. A graphic representation of this effect is seen in figure 1, where are shown the curve of diuresis of a normal dog (15.8 Kg.) in response to

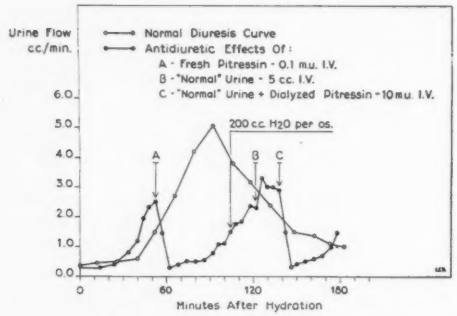

FIG. 1. A normal diuresis curve of the dog (weight 15.8 Kg.) and the antidiuretic effect of fresh Pitressin (A), normal urine (B), and normal urine plus dialyzed Pitressin (C).

the hydrating drink, and the curve of response when injections of Pitressin solution were given.

The test material was obtained by preparing urine of patients and of normal controls, collected over known periods (usually six to twelve hours) after the method of Ralli and associates.[3] Toluol as a preservative and sufficient 3% acetic acid to produce a pH between 6.0 and 6.5 were added. The entire sample was then evaporated by fan at room temperature within a twenty-four hour period to volumes between 80 and 100 cc. This was then dialyzed with agitation, for periods of six to twenty-four hours in casing containers† against cold running tap water. The final volume was determined and after filtration through filter paper, a portion equivalent to a fifteen-minute urine output period was used as the test dose. This was usually between 1.5 and 4.0 cc. This test dose was given intravenously following recovery of urine flow to diuretic levels from a preceding Pitressin dose. In some experiments (not shown in the figures), further injections of Pitressin were also given following the test injection, for evaluation of the reactivity of the animal to another known quantity of antidiuretic substance. No evidence was noted of untoward reaction, dyspnea, collapse, excitement, or other state which might be expected to influence urine production.

Urine specimens studied were secured from patients with chronic congestive failure and peripheral edema. Those with definite kidney diseases or independent liver diseases were excluded. Some patients had no preceding treatment with digitalis or mercurial diuretics; some had had digitalization but still presented definite evidence of decompensation; and others had had both therapeutic measures. Urine specimens from normal individuals were collected over measured intervals under normal conditions of hydration. In addition, Pitressin was added to some normal specimens which were then prepared in the usual manner.

RESULTS

In no instance did injection of physiologic saline or of urine from normal subjects produce an antidiuretic effect in dogs which had previously responded to Pitressin. Normal urine dialyzed after the addition of Pitressin would produce an antidiuretic effect only if large amounts (10 milliunits per cc.) of the drug had been added. No antidiuretic effect occurred after dialysis when the added Pitressin concentration was only 0.6 milliunit per cc. In figure 1 are shown the effects on the diuresis curve of fresh Pitressin, dialyzed normal urine and normal urine dialyzed after Pitressin addition (10 milliunits per cc.). It will be noted that both fresh and dialyzed Pitressin produced a fall in urine output of approximately equal amounts. Normal urine had no antidiuretic effect.

In table 1 are summarized the results obtained from the injection of urine from cardiac failure patients and the pertinent clinical data. A total of 15 patients were studied. The diagnoses included 7 of arteriosclerotic heart disease (ASHD), 5 of rheumatic heart disease (RHD), 5 of hypertensive heart disease (Hyp. H. D.), and 2 instances of cor pulmonale (Cor. Pulm.). One additional patient had cardiac failure of undetermined etiology. Five of the patients had multiple cardiac diagnoses.

Positive antidiuretic effects were obtained in

* Pitressin—Parke Davis Co.

† Visking #133—"Nojax" casing.

TABLE 1.—*Patients with Congestive Failure—Clinical Data and Antidiuretic Effect of Urine*

Case	Age	Sex	Diagnosis	B.P.	V.P.*	C.T.†	Edema	Liver	Prior Therapy	Urine Effect	Equivalence of Pitressin
1	45	M	RHD, Hyp.	170/105	190	30	1+	6 cm	None	pos.	0.4 m.u.
2	70	M	ASHD	120/80	195	33	3+	3	None	pos.	0.1 m.u.
3	72	F	Hyp. ASHD	170/120	—	—	3+	6‡	Digit.	pos.	0.4 m.u.
4	58	M	Cor. Pul.	140/70	300	30	4+	6‡	None	pos.	0.2 m.u.
5	64	F	ASHD	120/80	230	23	3+	4	Digit.	neg.	—
6	45	F	RHD	130/80	—	—	3+	6‡	Digit.	pos.	0.1 m.u.
7	59	M	ASHD Hyp.	160/100	—	—	3+	4	Digit.	pos.	0.3 m.u.
8	48	M	RHD	130/85	210	35	2+	7	None	pos.	0.5 m.u.
9	59	M	ASHD Cor. Pul.	115/80	—	—	4+	4	Digit.	neg.	—
10	72	M	ASHD	130/60	210	40	2+	4	Digit.	pos.	0.3 m.u.
11	48	M	? etiol.	115/95	270	50	3+	6‡	Digit. NH_4CL	pos.	0.6 m.u.
12	49	F	Hyp.	200/125	—	—	4+	?	Digit.	pos.	1.4 m.u.
13	70	M	Hyp. ASHD	180/125	270	—	4+	6	None	neg.	—
14	39	F	RHD	116/78	—	30	4+	7‡	Digit. Mercur.	pos.	0.4 m.u.
15	16	F	RHD	105/80	—	—	4+	3	Digit. Mercur.	pos.	1.5 m.u.

* Venous pressure in mm. saline
† Circulation time in seconds, arm to tongue (Decholin)
‡ Ascites present
m.u. signifies milliunits

12 cases, while no antidiuretic effects were noted in the urines of 3 patients, as can be seen in table 1. An estimate, proportional to the "area" of oliguria induced, of the antidiuretic potency (in terms of milliunits of pitressin activity) contained in fifteen minutes of urine output from these patients, is shown in the last column of table 1. Figure 2 presents the effect on the diuresis curve of fresh Pitressin and the typical effects of positive urines from cases 8 and 12. In figure 3 can be seen the graded effects of increasing doses of positive urine from case 6. In each instance, a definite and prolonged antidiuretic effect was obtained.

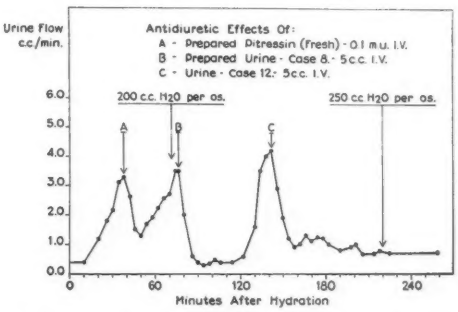

FIG. 2. The antidiuretic effect of fresh Pitressin (A), and prepared urine from case 8 (B) and case 12 (C). Dog weight, 15.8 Kg.

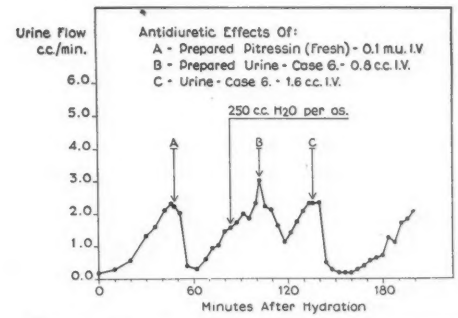

FIG. 3. The antidiuretic effect of increasing amounts of urine injected. 1.6 cc. given (C) produced about twice the effect of 0.8 cc. (B). Dog weight, 15.8 Kg.

DISCUSSION

The results of this study established the occurrence of antidiuretic factors in the urine excreted by patients in congestive failure. The identification of the source of these factors in the body, and assessment of the roles played in the genesis of failure remain problems for future attention. Review of the reports of Verney,[1] Pickford,[9] deBodo,[10] and others[11-15] supports the idea of a posterior pituitary origin for such antidiuretic factors, while the research of Heinbecker and White,[29] Walker,[16] and others[17-19] introduces the possibility of other mechanisms of water control. Shorr and others[21,32]

have given evidence of one such source in the liver.

We cannot identify the effective substance in "cardiac failure" urine as a posterior pituitary principle. Previous investigators[22] with Pitressin had reported that it dialyzed through membranes of the type used, the residual solution having decreased potency. We can report similar experience with commercial Pitressin. Figure 4 depicts our results with injections of Pitressin, freshly diluted and following dialysis. When dialyzed, an increase in the concentration of 100 times or more was necessary to produce the threshold responses obtainable with 0.1

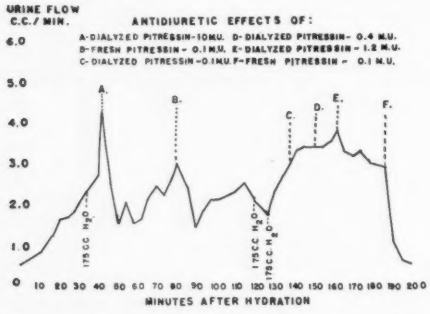

FIG. 4. The antidiuretic effect of increasing amounts of dialyzed Pitressin. No effect was produced until the dose given was raised to 1.2 m.u. (E) while 0.1 m.u. of fresh Pitressin caused a marked antidiuresis (B). Dog weight 12.2. Kg.

milliunits of nondialyzed Pitressin. The substance contained in cardiac failure urine, however, apparently lost no potency through the preparation and dialyzation process, nor did filtration remove the active principles. Although these methods of preparation of urine have been recently challenged,[33] it would appear that the effective substance is not identical with commercial Pitressin.

The question of the role of these substances in the development of cardiac failure is even more difficult to clarify. Many observers have indicated that in cases of congestive failure, there is a disturbance of the normal metabolism of electrolytes and water leading to sodium retention and ensuing increased fluid volume.[7,8,23–25] Investigation of the effect of cardiac failure urine containing antidiuretic substances on sodium excretion by the test animal is contemplated.

The evidence presented here strongly indicates the occurrence of an antidiuretic substance or substances in the urine of some patients with cardiac failure, which may be important in the retention of fluid in this condition. To the list of clinical syndromes in which antidiuretic substances have previously been reported, namely cirrhosis,[3] acute hepatitis,[20] nephrotic edema,[2] acute hemorrhagic nephritis,[2] eclampsia and other toxemias of pregnancy,[4] Cushing's syndrome,[2] premenstrual edema,[2] dehydration,[12] and hypertension,[33] congestive failure may well be added.

SUMMARY

1. An antidiuretic effect was induced in hydrated dogs by the intravenous injection of concentrated dialyzed urine of 12 of 15 patients with congestive heart failure. No such effect was exerted by urine of normal controls.

2. Evidence was obtained that the antidiuresis could not be attributed to a substance with the characteristics of commercial Pitressin.

ACKNOWLEDGMENTS

We wish to express our gratitude to Dr. H. L. White for advice in these investigations.

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Arterioles of Kidney and Pancreas in Cases of Cardiac Hypertrophy of Undetermined Causation

By HAROLD A. FERRIS, JR., M.D.

The arterioles in the kidneys and pancreas in 50 consecutive necropsy cases of cardiac hypertrophy of undetermined cause and in 50 control cases were measured and studied histopathologically in an effort to determine the cause of the cardiac hypertrophy. The weight of the heart, the ventricle affected by hypertrophy and the age of the patient also were recorded in each case and correlated with the changes in the ratio of the wall to lumen in the arterioles. This study revealed that in about 40 per cent of cases the cardiac hypertrophy was probably due to antecedent hypertension.

CARDIAC hypertrophy with recordings of normal arterial blood pressure is commonly considered to be the result of arterial hypertension at periods other than when the blood pressure recordings were made. The work of Kernohan, Anderson, and Keith,[1] Morlock,[2] Cain,[3] and Pilcher and Schwab[4] has shown diffuse arteriolar disease in cases of arterial hypertension, and it would seem advisable to study the arterioles in representative organs in cases of cardiac hypertrophy of undetermined cause to record any hypertensive changes that may be present.

Accordingly, 50 consecutive cases of cardiac hypertrophy of undetermined cause were chosen from the necropsy records at the Mayo Clinic. The ages of the patients at the time of death ranged from 30 to 85 years and the hearts weighed at least 50 Gm. more than the maximal normal weight, according to H. L. Smith's formula,[5] and were based on protocols of the clinic from 1931 to 1946. The actual heart weights are tabulated in table 1. The blood pressure was neither more than 150 mm. of mercury systolic nor more than 90 mm. diastolic in these cases. The usual causes of myocardial hypertrophy were excluded, such as hypertension, cardiac valvular disease, chronic cor pulmonale, thyrotoxicosis, and congenital defects. Fifty control cases in which the ages of patients ranged from 21 to 78 years were studied during the same period. In these cases heart weight and blood pressure were normal; cardiac, renal or systemic diseases were not found.

TABLE 1.—*Heart Weight in Grams in Cases of Undetermined Cardiac Hypertrophy*

Weight range	Number of cases
301–350	2
351–400	5
401–450	14
451–500	12
501–550	10
551–600	5
601–650	1
651–700	0
701–750	1
Total	50

METHOD

Four sections were made from the kidneys and four from the pancreas in each case. These were fixed in 10 per cent solution of formalin, blocked in paraffin, and stained. The sections were stained by the hematoxylin and eosin, the van Giesen, Mallory-Heidenhain, or the Elastin H. method, and measurements were made of the arterioles. To prevent bias, I arranged the work so that I would not know to which group the particular section in question belonged, while these measurements and computations were being made. Using the method of Kernohan, wall-to-lumen ratios were computed on arterioles varying in outside diameter from 25 microns to 100 microns. Six arterioles were measured in each section, making a total of 24 arterioles from the kidneys and 24 arterioles from the pancreas in each case. A Bausch and Lomb micrometer ey-

From the Division of Medicine, Mayo Clinic, Rochester, Minn.

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piece was used over a high power objective, obtaining a magnification of 450. The wall of each vessel was measured in areas which appeared to be cut at right angles to its course as in figure 1, that is *ab*, *cd*, *ef* and *gh*, and the lumen in two diameters, that is, *bc* and *fg*. Then the average width of the wall and lumen of each vessel was computed. Finally, the wall-to-lumen ratio was determined for each vessel; then the average wall-to-lumen ratio for each kidney and pancreas was computed. Since sections from the control cases and from cases of cardiac hypertrophy were subjected to similar methods and since

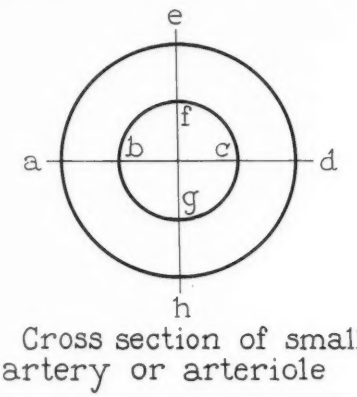

FIG. 1. Method of measuring an arteriole.

this is a comparative study, it does not seem likely that laboratory methods will enter as an important source of error.

RESULTS

The distribution of wall-to-lumen ratios for kidney and pancreas in cases of cardiac hypertrophy of undetermined origin and in control cases is given in table 2. It will be noted that for the kidney in only 3 (6 per cent) of the control cases was the wall-to-lumen ratio less than the normal ratio of 1:2, whereas in 35 (70 per cent) of the cases of cardiac hypertrophy it was below 1:2. The wall-to-lumen ratio in arterioles in the pancreas was less than 1:2 in only 4 (8 per cent) of the control cases and in 23 (46 per cent) of the cases of cardiac hypertrophy. In 20 (40 per cent) of the cases of cardiac hypertrophy the wall-to-lumen ratio of the arterioles was less than the normal ratio of 1:2 in both kidney and pancreas.

The histopathologic findings of the vessels studied varied from essentially normal to those characteristic of hypertension. Several of these vessels are shown in figure 2. In general, vessels in which the wall-to-lumen ratio was less than 1:2 show evidence of intimal proliferation, thickening of the media by hypertrophy of smooth muscle or by hyaline replacement of the media.

The distribution curve of wall-to-lumen ratio according to age of patients in decades in cases of cardiac hypertrophy and in controls in kidney and pancreas are given in figures 3 and 4. There appears to be no relationship between wall-to-lumen ratio and age.

TABLE 2.—*Distribution of Wall-to-Lumen Ratios of Arterioles of Kidneys and Pancreas in Cases of Cardiac Hypertrophy and in Controls.*

Ratio of wall-to-lumen	Kidney		Pancreas	
	Cardiac hypertrophy	Controls	Cardiac hypertrophy	Controls
1:1.2			1	
1:1.3	3		1	
1:1.4	4		2	
1:1.5	7		2	1
1:1.6	3		4	1
1:1.7	8	1	4	
1:1.8	6	2	4	1
1:1.9	4		5	1
1:2.0	8	4	4	6
1:2.1	2	5	3	7
1:2.2	2	6	2	5
1:2.3	2	11	5	3
1:2.4		4	4	5
1:2.5		8	4	3
1:2.6		2	2	4
1:2.7			2	2
1:2.8		2		6
1:2.9	1	2		1
1:3.0		2		1
1:3.1				1
1:3.2				1
1:3.3				
1:3.4		1		1
1:3.5			1	

The number of cases of cardiac hypertrophy of unknown etiology in which thickness of the left ventricle only, the right ventricle only, or both left and right ventricles was increased was determined. The upper limits of normal for the thickness of the left ventricle is considered to be 1.5 cm. and for the right ventricle 0.4 cm. The average arteriolar wall-to-lumen ratio for kidney and pancreas was correlated

with these groups. The results are shown in table 3.

It is noted incidentally that 29 (58 per cent) of the patients showed coronary sclerosis of grade 2 or more, using grade 0 as meaning no sclerosis and grade 4 as meaning complete closure of the vessel. Eleven of these patients (38 per cent) presented wall-to-lumen ratios below 1:2 in both kidney and pancreas. Sixteen (32 per cent) of the patients showed evidence of chronic myocardial infarction. Among this group 5 patients (31 per cent) presented wall-to-lumen ratios below 1:2 in both kidney and pancreas.

Among the cases of undetermined cardiac hypertrophy in which no evidence of arteriolar sclerosis was found, 18 or 60 per cent had coronary sclerosis of grade 2 or more, 4 or 13 per cent had congestive heart failure, and 7 or 23 per cent had mild anemia.

Ten of the 50 cases of undetermined cardiac hypertrophy had only one blood pressure re-

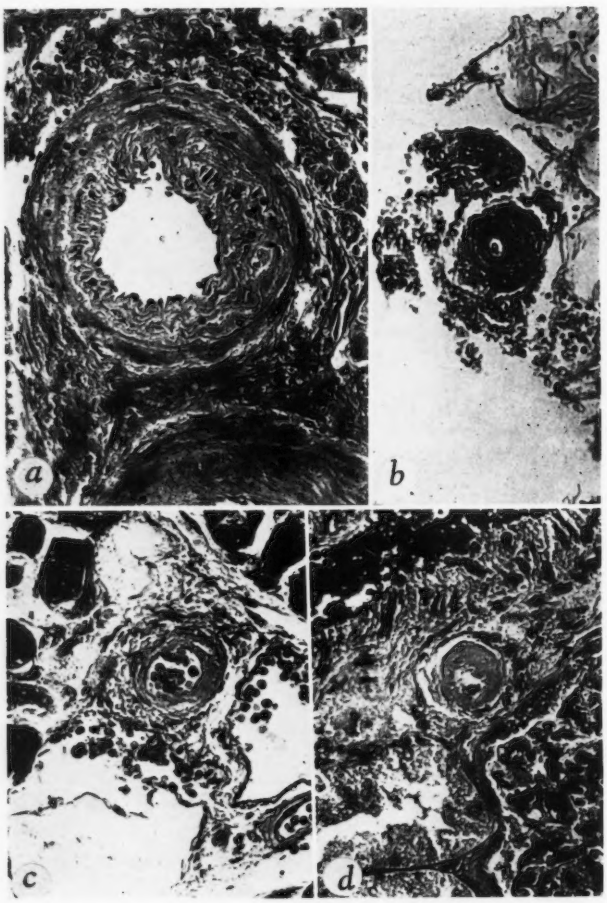

FIG. 2. *A*. Small artery in kidney, showing moderate intimal proliferation (hematoxylin and eosin, ×235). *B*. Arteriole in pancreas of another case showing marked medial hypertrophy (hematoxylin and eosin, ×205). *C*. Arteriole in pancreas showing hyaline replacement of media (hematoxylin and eosin, ×320). *D*. Arteriole in kidney showing hyaline replacement of media (hematoxylin and eosin ×320).

cording. Among this group it was found that 4 cases or 40 per cent had wall-to-lumen ratios

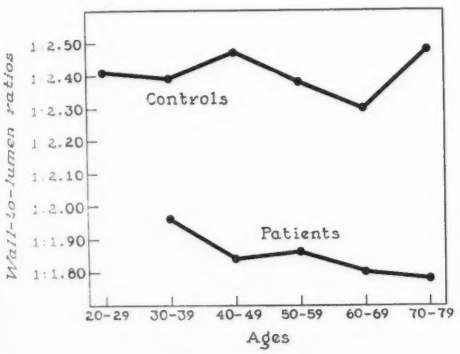

FIG. 3. Distribution wall-to-lumen ratios of arterioles in kidney according to age in decades.

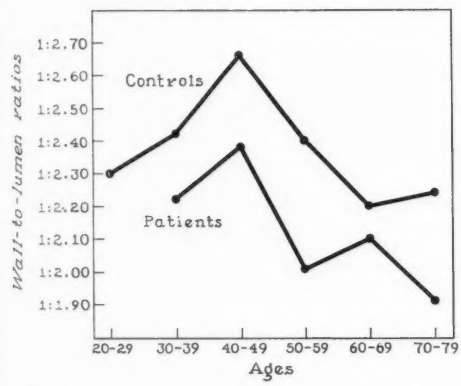

FIG. 4. Distribution wall-to-lumen ratios of arterioles in the pancreas according to age in decades.

TABLE 3.—*Increased Thickness of Ventricle in 50 Cases of Cardiac Hypertrophy: Average Ratio of Wall-to-Lumen.*

Increased thickness of:	Cases	Per cent	Average ratios of wall-to-lumen arterioles of:	
			Kidney	Pancreas
Left ventricle	11	22	1:1.87	1:2.05
Right ventricle	7	14	1:2.13	1:2.34
Both ventricles	6	12	1:1.60	1:1.97

below 1:2 in both kidney and pancreas. This compares with the findings in cases having multiple blood pressure recordings.

COMMENT

A study of the arterioles of the kidneys and pancreas in 50 cases of cardiac hypertrophy of undetermined cause shows wall-to-lumen ratios in both kidney and pancreas of less than the normal ratio of 1:2 in 20 cases (40 per cent). These ratios bear no relationship to age. The arterioles having wall-to-lumen ratios of less than 1:2 demonstrate pathologic changes found in arterial hypertension. The increased weights of the hearts studied were due to generalized hypertrophy of the heart; in only 11 cases (22 per cent) was the thickness of the left ventricle alone increased and in only 7 cases (14 per cent) was the thickness of the right ventricle alone increased.

Kaplan, Clark and de la Chapelle[6] reviewed 43 cases of congestive heart failure with predominant left ventricular hypertrophy of unknown origin and studied the arterioles of the kidney and adrenal gland. In 30.9 per cent of these cases mild or severe renal arteriolar sclerosis was present. Of 269 patients without hypertension also studied by these authors 12 per cent showed renal arteriolar sclerosis which bore a relationship to age. Of 154 patients having essential hypertension, 82.5 per cent of those dying in congestive heart failure showed renal arteriolar sclerosis. These authors concluded that although the role of antecedent hypertension cannot be excluded in the individual case of hypertrophy of the left ventricle of unknown cause its absence in the majority of these cases seems likely.

Moritz and Oldt,[7] using Kernohan's technic, obtained wall-to-lumen ratio in arterioles of controls from 1.0 to 1.9 and in arterioles of hypertensives from 1.0 to 1.36. The distribution curves of these ratios showed a wide overlapping with only 29 per cent of hypertensives having a wall-to-lumen ratio less than that seen in any control.

Gross and Lisa[8] give strong support for considering hypertension as the cause for undetermined cardiac hypertrophy by reporting renal arteriolar sclerosis in each of 18 cases of cardiac hypertrophy with normal blood pressure and moderate to severe coronary disease.

Conclusions

From the present study it seems that 40 per cent of cases of cardiac hypertrophy of undetermined origin are probably due to antecedent hypertension. This study, however, does not throw any light on the cause of cardiac hypertrophy of unknown origin in cases encountered at necropsy when sclerosis of the arterioles in various organs cannot be demonstrated.

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Intrabronchial Electrocardiography
A Preliminary Report

By PAUL H. LANGNER, JR., M.D., AND JOSEPH P. ATKINS, M.D.

The Einthoven hypothesis implies that differences in the conductivity of body tissues are not sufficiently great to invalidate the concept that the body is a homogeneous volume conductor. Some investigators believe the lungs are sufficiently poor conductors to make questionable the concept that the body can be regarded as a homogeneous volume conductor. Intrabronchial electrocardiography is presented as a possible method for studying this problem. In ten individuals without manifest cardiac disease the distribution of potential variations in the lungs as manifested by the QRS complexes corresponded approximately and qualitatively with the distribution of the QRS complexes recorded from the body surfaces.

IT IS the purpose of this paper to describe our preliminary experiences with the technic of intrabronchial electrocardiography. We were prompted to employ this method for the investigation of the distribution of potential variations associated with cardiac contraction in the hope of being able to obtain evidence for or against the field theory[1, 2] of electrocardiography.

MATERIAL AND METHODS

In 4 anesthetized dogs a No. 8 ureteral catheter with an electrode at the tip was passed through a tracheotomy tube into the periphery of the bronchial tree. In 5 human subjects a bronchoscopic forceps insulated except at the tip was introduced through a laryngoscope. In one of these, fluoroscopic guidance was used to check the position of the electrode; in the others, this position could be roughly estimated. In 5 human subjects a No. 8 ureteral catheter with an electrode at the tip was passed without instrumentation through the oropharynx, larynx and trachea into the bronchi and the position of the electrode was observed fluoroscopically in the anteroposterior and lateral views and recorded on x-ray films. Basal sedation with pentobarbital and topical anesthesia with 1 per cent cocaine were used in the human subjects. In the last 4 human subjects studied all electrocardiograms and films were made in the upright position. In the other subjects all studies were made in the recumbent position. It is very important to keep the position of the body and the phase of respiration constant when comparing the leads from the surface of the body with leads made from within the left lung. It is well known that extremity leads can be made to vary in amplitude and contour by changes in respiration and body position, the degree of variation depending upon the individual subject. Furthermore we found that aV_L varied significantly even when the position of the shoulders was changed with relation to the body. Failure to control these sources of variation would lead to gross error in evaluation of results. All records were made on a direct writing electrocardiograph.* Attention should be called to the fact that the postero-anterior x-ray film does not supply sufficient information to localize the electrode. It frequently lies in the posterior portion of the lung and therefore may be farther from the heart than would seem to be the case in the postero-anterior film. The length of the time available for intrabronchial exploration is limited by the duration of the anesthesia and the radiographic exposure.

The intrabronchial potential variations were recorded, using a central terminal[3] as an "indifferent" electrode and were compared with central terminal leads from the extremities, the standard precordial positions, and other exploratory leads from the thoracic wall, abdomen, and back.

RESULTS

From the left lower lobe bronchi positive QRS complexes were obtained in both human subjects and dogs which were intermediate in size between that of the largest complex obtained from a precordial position (usually V_4 or V_5) and that obtained from the left mid or posterior axillary position taken at the same level as the intrabronchial electrode. As the electrode was withdrawn upward toward the bifurcation of the trachea the QRS complex became negative. From the right lung the QRS complexes were principally negative and were intermediate in size between V_1 and V_2 and leads from the right mid axilla taken at the same level as the intrabronchial electrode (See figures 1–2–3).

From the Medical Department of the Provident Mutual Life Insurance Company and the Department of Medicine and Broncho-esophagologic Clinic of the University of Pennsylvania School of Medicine.

* Viso-cardiette, The Sanborn Company.

In four individuals extensive body exploration was performed. The electrical field of the heart as manifested by the body-surface QRS complex patterns was mapped out. This field could be divided into a predominantly positive zone manifested chiefly by R waves, a predominantly negative zone manifested chiefly by S waves or Q waves, and an intermediate or transitional zone of equally biphasic patterns extending in a fairly regular manner between the positive and negative zones. This field was usually eccentric, having a larger negative than positive zone. This distribution of surface patterns has previously been described by Ashman and associates[4] and Grant.[2] For purposes of orientation the transitional zone of the QRS complex obtained on the body surface was visually extended as a plane projecting through the body and dividing it into positive and negative zones. When the intrabronchial electrode lay clearly on the positive side of the transitional zone the complexes recorded were positive consisting chiefly of R waves. When the intrabronchial electrode lay clearly on the negative side of the transitional zone the complex was chiefly negative consisting of an S or a Q wave. When the electrode was in or very near the projection of the transitional zone the complexes were equally biphasic.

FIG. 1.—Intrabronchial electrode in left lower lobe bronchus. Anterior and posterior margins of the body-surface QRS transitional zone are indicated by lower and upper radiopaque bands respectively.

In figure 1 the opaque band diagonally across the left lower lung field represents the anterior margin of the body-surface transitional zone and the upper band represents the posterior margin of the transitional zone. The imaginary plane of the transitional zone extends from the lower band upward and backward through the lung to the upper band. The intrabronchial electrode is seen behind the lower band but since the electrode is half way between the anterior and posterior chest wall it lay clearly below the transitional zone plane at that point and recorded the positive complex shown in figure 2. The biphasic complex in figure 2 was recorded when the electrode was withdrawn to a position about one-half the distance between the upper and lower bands, and above this negative complexes were obtained. From the middle of the right lung a negative complex was obtained as shown in figure 2. Figure 3 represents the records of another individual obtained by intrabronchial exploration similar to that described for figures 1 and 2.

In one individual with an unusually vertical heart we were unable to introduce a No. 8 catheter into the left lower lung field far enough to reach the positive side of the transitional zone and therefore only negative complexes were obtained. In an individual with a horizontal heart positive complexes were obtained not only from a left lower lobe bronchus but also from a left upper lobe bronchus as shown in figure 3.

At this point we can not say whether the transitional zone is always a fairly regular plane or a zone of variable regularity and depth. To determine this would require further study which we expect to undertake in the near future.

SUMMARY AND CONCLUSIONS

1. The technic of intrabronchial electrocardiography provides a means of exploring an interesting region of the body, the lungs, the electrical properties of which are a matter of controversy.[5] We have obtained the same type of information from lung puncture in dogs with a solid needle insulated except at the tip but we believe the intrabronchial method is more physiologic and obviates the possible complications of pneumothorax and intrapulmonary hemorrhage.

2. While the analysis of our results so far has been limited to the contours of the QRS complex rather than absolute magnitude the

results indicate that the distribution of potential variation in the lungs corresponds approximately and qualitatively with the distribution of potential variations recorded from the body surface.

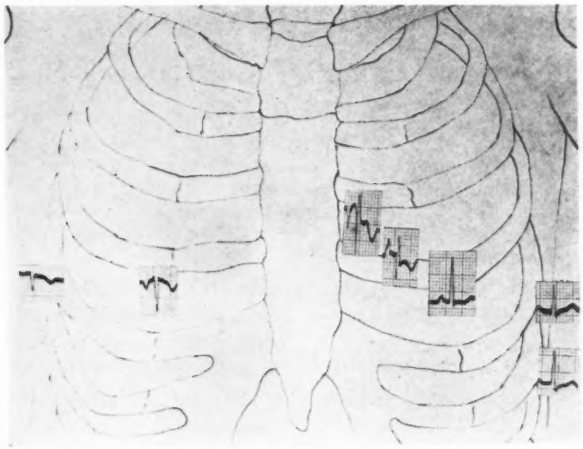

FIG. 2

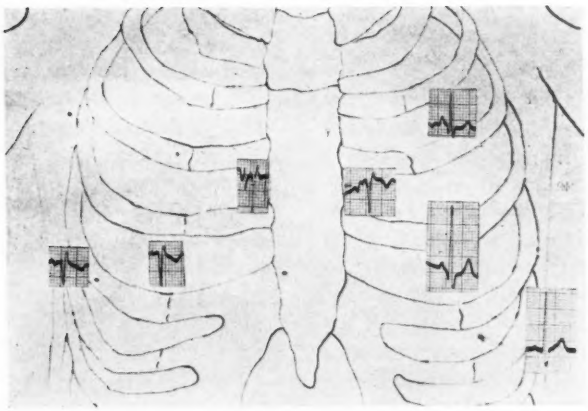

FIG. 3

FIGS. 2 AND 3.—Comparison of QRS complexes from body surface with those recorded from the bronchi. The complexes mounted along the lateral chest margins were taken from the mid-axillary regions of the body surface. All the other complexes are mounted overlying the approximate position of the intrabronchial electrode from which they were recorded.

3. Intrabronchial electrocardiography would seem to be a useful technic to determine whether the cardiac action currents are distributed to the body surface by preferential pathways or throughout the body as though it were an approximate field.

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Paroxysmal Ventricular Tachycardia with Second Degree V-A Block and Reciprocal Rhythm

By SIDNEY GRAU, M.D., AND JAMES L. GOUAUX, M.D.

An instance of paroxysmal ventricular tachycardia with retrograde conduction is presented. This occurred in a patient in the terminal stage of arteriosclerotic heart disease. The electrocardiograms obtained during this period, representative portions of which are illustrated, were unique in that reciprocal beats and fusion beats were noted; the latter being unusual because of the origin and site of fusion of the impulses. A hitherto unreported abnormality of the retrograde P wave is also described and illustrated.

THE OCCURRENCE of paroxysmal ventricular tachycardia exhibiting second degree V-A block with the Wenckebach phenomenon is a rarity in clinical electrocardiography.[1–5] It is the purpose of the present report to add another case in which this arrhythmia was associated with reciprocal rhythm and to cite an abnormality of the retrograde P wave that has been hitherto undescribed.

MATERIAL

The following representative electrocardiograms were taken during the last three days before death in the case of a 76 year old physician who was admitted to the hospital because of severe congestive failure secondary to arteriosclerotic heart disease. Until the last twenty-four hours before death, the patient remained conscious and alert. His course in the hospital was complicated by frequent episodes of paroxysmal ventricular tachycardia. Treatment with digitalis was instituted with extreme caution in order to avoid conversion of the arrhythmia to ventricular fibrillation. All attempts to control the arrhythmia with quinidine, both orally and intravenously, were futile. He was questioned during the paroxysms of ventricular tachycardia, but no symptoms that might have been attributed to the change in cardiac rhythm were noted by him.

Several long strips both of the sinus rhythm and the ventricular tachycardia were taken. The interpretation arrived at and illustrated by the portions of the electrocardiograms shown are based on careful analysis of these longer strips. The paroxysms were, in general, characterized by the following features:

1. *Abrupt Change in the Electrical Axis o QRS.* It is well known that the shift of the electrical axis as illustrated in figure 1 may be altered, among other things, by aberrant ventricular conduction initiated either by supraventricular conduction defect, intraventricular block or by an idioventricular pacemaker. In figure 1 the electrical axis of QRS during the sinus rhythm is −65 degrees, while during the paroxysms it is +115 degrees.

2. *V-A Block.* As the paroxysms of tachycardia were being recorded instances were noted in which 1:1 retrograde conduction occasionally occurred (fig. 2). This was the exception rather than the rule, the more frequent occurrence being retrograde conduction with second degree V-A block and progressive prolongation of the R-P interval, i. e. the Wenckebach phenomenon (figs. 3 and 4). In figure 3 it can readily be seen that no constant relation between the ventricular beats and the retrograde P wave exists owing to the V-A block that is present. The R-P interval becomes progressively longer (from 0.19 second to 0.30 second)

From the Department of Medicine, Veterans' Administration Hospital, Bay Pines, Florida.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

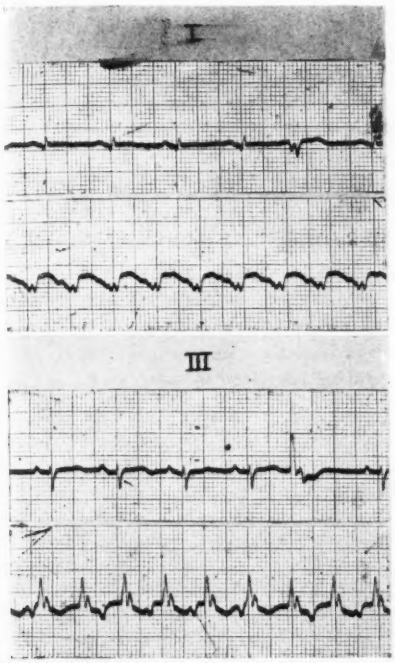

FIG. 1. Representative tracings of Leads I and III during sinus rhythm and paroxysmal ventricular tachycardia showing the marked change in electrical axis of QRS from −65 degrees to +115 degrees.

and finally an auricular beat is missing, giving rise to 8:7 retrograde conduction. In figure 4 essentially the same mechanism is depicted except that here the retrograde conduction varies from 6:5 to 5:4.

3. *Reciprocal Beats and Fusion Beats.* During the paroxysms of tachycardia three types of

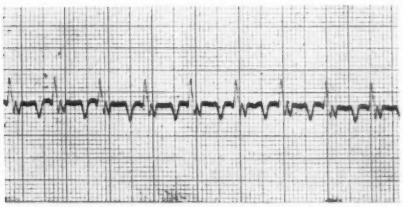

FIG. 2. Paroxysmal ventricular tachycardia (Lead II) with 1:1 retrograde conduction. Rate 143.

ventricular complexes are seen; the first being of idioventricular origin characterized by a prolonged QRS complex occurring at a regular rate of 143 per minute; the second, occurring prematurely, showing complexes of normal QRS duration and identical in contour with the sinus beats at the time of sinus rhythm (fig. 5); the third having a contour and QRS duration intermediate between the first and second types

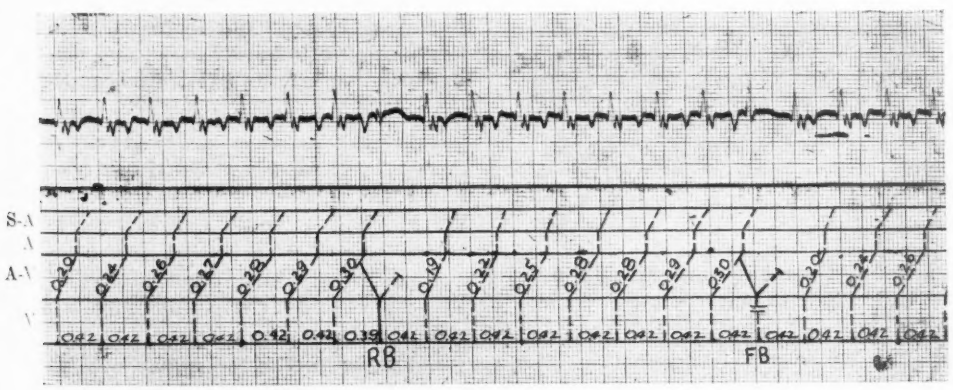

FIG. 3. Paroxysmal ventricular tachycardia (Lead II) showing partial retrograde heart block (8:7 conduction) and exhibiting the Wenckebach phenomenon. Examples are shown of a reciprocal beat, fusion beat, and the changing size of the P waves. The mechanism is illustrated in the diagram below the electrocardiogram. The values for the R-R intervals are written horizontally; the values for the R-P intervals diagonally. Retrograde impulses are indicated by broken lines; reentrant impulses by solid lines. RB and FB indicate the reciprocal beat and fusion beat respectively. S-A indicates the impulse spread between the sinus node and auricles. A-V indicates the impulse spread between the auricle (A) and the ventricle (V). Discussed in text.

and occurring at the time when an idioventricular beat is expected. The 'premature' beats occurred 0.03 second earlier than the expected idioventricular beats and occurred throughout the records only after the longest R-P intervals; for that reason they were interpreted as reciprocal beats due to re-entry of the delayed retrograde impulse. The following idioventricular beat was characterized by a shortened retrograde conduction time, measuring 0.18 to 0.20 second. The possibility that the 'premature' beats were merely nodal premature systoles was considered. This possibility was discounted when it was realized that they occurred only when a reciprocal beat was expected. Those beats with a QRS complex intermediate between that of the idioventricular beats and that of the reciprocal beats are best accounted for by assuming fusion of the idioventricular impulse occurring at the expected time with a reciprocal impulse expected because of the long R-P interval preceding that beat. These fusion beats are identical in origin and site of fusion with those described as unusual instances of fusion of two impulses of identical origin in a case of Malinow and Langendorf.[4]

4. *Double Re-Entry.* Of particular interest were some instances (fig. 4) where a fusion beat was followed by a reciprocal beat indicating that re-entry to the ventricles occurred twice in succession, i. e. the re-entrant impulse performed a second re-entry; since there is a retrograde P wave between the fusion beat and the reciprocal beat we have clear evidence for the second re-entry in the A-V junction. It would be impossible to explain the retrograde P wave by retrograde conduction of the idioventricular impulse which fuses with the first reciprocal impulse in the ventricles and is prevented from reaching the A-V junction. Such multiple re-entry, true reciprocal rhythm and not merely isolated reciprocal beats, is most unusual in the human heart.[6, 7]

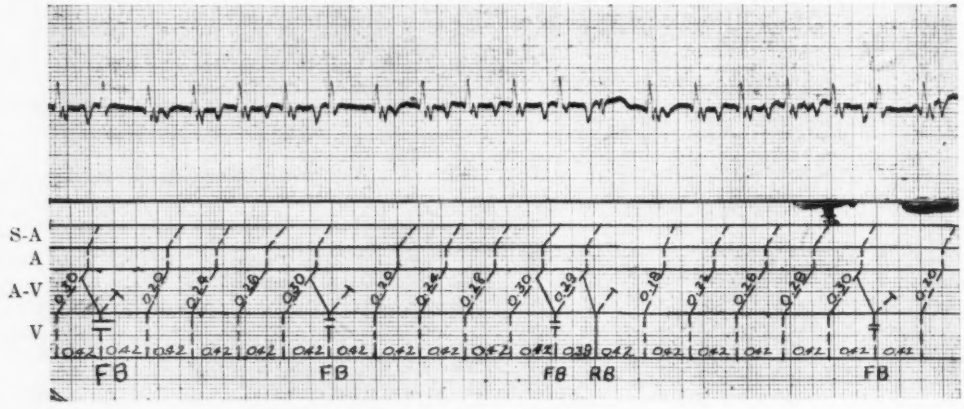

FIG. 4. Example of a fusion beat followed by a reciprocal beat, illustrating the phenomenon of double re-entry. Discussed in text. Conventions as in figure 3.

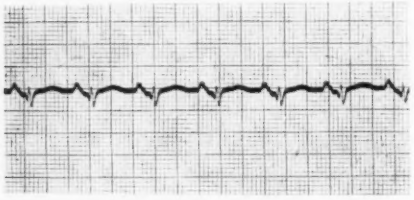

FIG. 5. A portion of Lead II taken during sinus rhythm.

5. *Varying Size of the Retrograde P Wave.* In all the tracings of the tachycardia in which the Wenckebach phenomenon was present, the retrograde P wave became progressively larger. This is adequately seen in figures 3 and 4 where the depth of the retrograde P wave increases as the R-P interval lengthens, so that the P wave inscribed before the dropped auricular beat appears as the largest. No adequate

explanation can be offered at the present time for this rarity. It was at first considered by us that the variation in size was due to the superimposition of the P wave on the T wave. This does not seem probable for the T waves of those beats (reciprocal, fusion and idioventricular which showed no retrograde conduction were practically isoelectric. Therefore, they could not account for the change in the P-wave size. The most probable explanation for this phenomenon is that it is an unusual occurrence of aberrant retrograde conduction, manifested by progressively more bizarre and prolonged P waves, and is associated with the Wenckebach phenomenon.

Conclusions

A case of paroxysmal ventricular tachycardia occurring in an elderly white man with severe arteriosclerotic heart disease is described. The tachycardia was considered to be noteworthy because of the following characteristics:

(1) Second degree V-A block with the Wenckebach phenomenon.

(2) The occurrence of both reciprocal beats and fusion beats during the tachycardia. The latter were unusual in that the origin of the fusing impulses and the site of their fusion was within the ventricles.

(3) Evidence of re-entry occurring twice in succession; constituting a miniature circus movement.

(4) A progressively increasing depth of the retrograde P waves which has, as far as can be ascertained, never been previously reported. At present no adequate explanation for this rare occurrence can be offered except that it may be due to aberrant retrograde conduction associated with the lengthening R-P interval (Wenckebach phenomenon).

ACKNOWLEDGMENT

The authors are indebted to Dr. Richard Langendorf of Chicago, Illinois, for his invaluable advice and criticism in the preparation of this paper.

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Transfixion of the Heart by Embedded Ice Pick Blade with Eight Months' Survival

By HARRY J. LOWEN, M.D., SEYMOUR A. FINK, M.D., AND MILTON HELPERN, M.D.

A case is presented of a 24 year old Puerto Rican man whose heart was transfixed by the anterior end of an ice pick blade, with the posterior end of the blade fixed in the body of the sixth dorsal vertebra. The patient survived for eight months. Roentgenologically, the patient presented a problem in determination of the path of the foreign body. At autopsy, vegetations were found in the heart on the perforated mitral valve; these were the source of multiple embolizations.

REVIEW of the literature reveals many cases of penetrating wounds of the heart caused by a variety of objects. However, the percentage of these cases involving the auricle alone is small and of these latter the number with recorded electrocardiographic tracings is even less.

Middleton,[1] in a review of the literature, could find only 4 cases with electrocardiograms[2–4] and added one case of a stab wound of the right auricle (Case 2). There were also a few other reports published at about this time. Harken and Zoll[6] report a case of empyema due to injury by a shell fragment which, at operation, showed the empyema to communicate with a laceration in the pericardium and underlying adherent left auricle; the laceration of the auricle was plugged by a large infected intracardiac hematoma. Noth[7] reported a case of stab wound of the left atrium (Case 18). Herve and Forero Sarabia[8] published 5 cases of auricular wounds, with electrocardiograms summarized in a table, but only two reproduced. The electrocardiographic changes in these cases are not repeated here because they were not specific for auricular damage and were more suggestive of pericarditis than infarction.

The following case is reported because it is unique in that the foreign body was fixed while the pulsating heart moved constantly upon it.

CASE REPORT

R. A., a 24 year old Puerto Rican man, was admitted to the Urological Service of Harlem Hospital on February 5, 1947. His principal complaints were chills, fever, and pain in the left costovertebral angle radiating down to the left thigh, for the previous thirty-six hours. In addition, he had dysuria and noted the urine to be cloudy but had passed no stones.

Physical examination revealed a well developed and well nourished man who was acutely ill. The principal findings were exquisite tenderness in the left costovertebral angle, and tenderness in the left lower abdominal quadrant. The heart was regular with a rate of 60 and murmurs of moderate and identical intensity were heard throughout systole and diastole. In the upright position, these were heard loudest posteriorly at the level of the fourth and fifth thoracic vertebrae and equally on both sides in the interscapular area; and with the patient in the prone position, the murmurs were loudest on the right side at these same levels. Systolic and diastolic murmurs were also heard in the anterior axillary line at the level of the fifth intercostal space on the right side anteriorly and a rough systolic in addition to a long faint systolic was heard all over the left precordium. The urine on admission revealed a one plus albumin and a few white blood cells per high power field. The blood count showed 9,200 leukocytes with a differential of 70 per cent polymorphonuclear leukocytes, 28 per cent lymphocytes and 2 per cent monocytes. The hemoglobin was 70 per cent; the red blood cells 3,700,000. The diagnosis on admission was pyelonephritis.

Because of the cardiac murmurs, a medical consultation was called and a routine fluoroscopy revealed a slender metallic object pointing anteriorly from the mid-dorsal area in the region of the left auricle. On further questioning, the patient disclosed that he had been stabbed twice in the back with an ice pick about six months previously. Evidently, the handle of the ice pick had broken off, of which he was unaware, and the blade had remained within his thorax. After the accident he had presented himself at the emergency ward of a hospital where he refused to remain and signed himself out subsequently. There were two small scars visible on the back in the interscapular area, one near the spine of the left

From the Medical Service of Harlem Hospital, New York, N. Y., and the Office of the Chief Medical Examiner of New York City.

scapula and the other just over the posterior end of the buried ice pick blade.

After a few days of bed rest, during which 40,000 units of penicillin were administered every three hours, the patient became asymptomatic. Several subsequent urine specimens revealed albumin and red blood cells. Smears of the urine revealed no organisms; on culture, gamma streptococcus and colon and paracolon bacilli were identified. An intravenous pyelogram was negative. Roentgenograms of the chest in posteroanterior and lateral positions were reported as showing "the presence of a linear, pointed, metallic foreign body, resembling an ice pick, located to the left of the spine between the eighth and ninth ribs, running posteroanteriorly and extending as far as the upper portion of the left auricle; it may extend through the thoracic aorta but there is no evidence of dilation at this point." The instrument lay to the left of the seventh dorsal vertebra in a longitudinal plane pointing directly forwards. It had caused some bone production around it, indicating that it had penetrated the bone. A barium drink revealed displacement of the esophagus to the right at the level of the ice pick blade and it was the impression of the roentgenologist that it might have penetrated the aorta (fig. 1). The electrocardiograms (fig. 2) were interpreted as revealing a posterior wall myocardial infarction.

Eighteen days after admission, the patient developed a sudden onset of dizziness associated with inability to use the right upper and lower extremities. Neurologic examination revealed signs consistent with a right hemiplegia. The following morning a neurologic consultant diagnosed a right hemiparesis and, because the signs were transitory, cerebral embolism was considered the most likely cause.

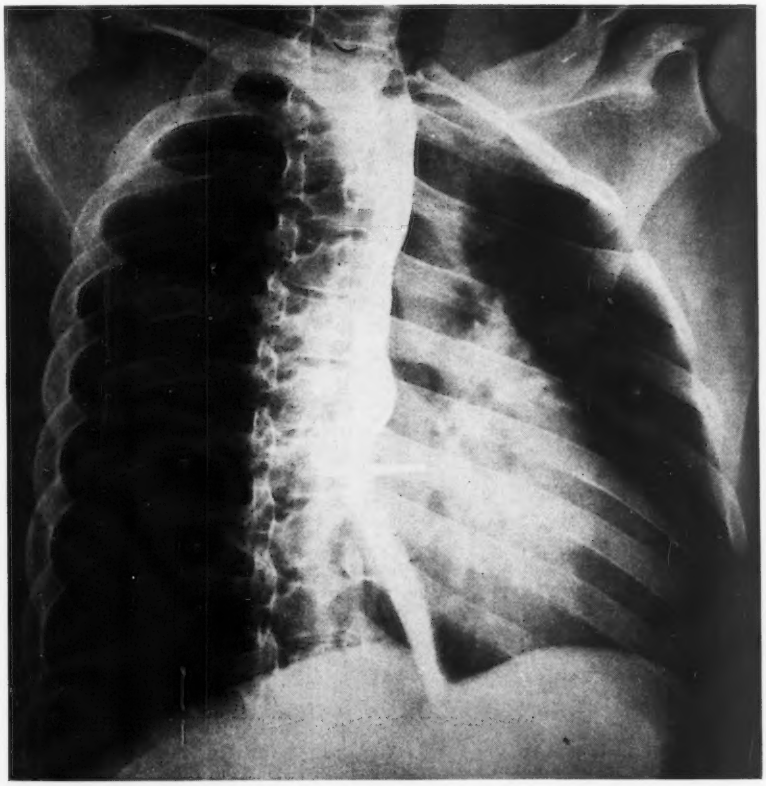

FIG. 1.—Right oblique view, with barium in esophagus and ice pick in situ.

On the fortieth day after admission, an angiocardiogram (fig. 3) was done by Dr. Sussman of Mount Sinai Hospital and his report was as follows: "Examination of the chest, including angiocardiography, shows a metal spike which enters the left posterior chest immediately adjacent to the spine. In both the lateral and posterior-anterior views, the spike appears to pass through the descending aorta, the tip impinging in the region of the left auricle. It might, however, pass very close to the aorta, rather

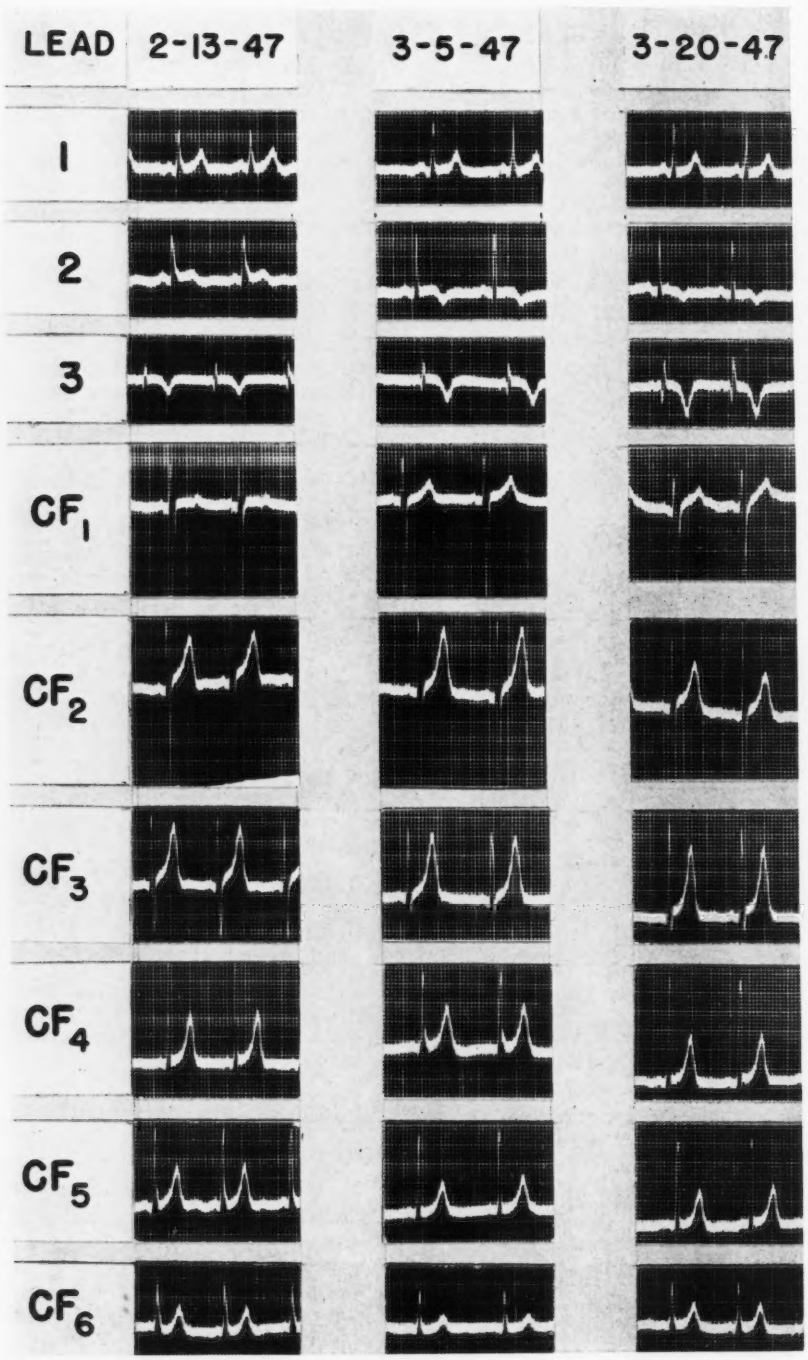

FIG. 2.—Electrocardiograms of the patient.

than through it. The cardiac chambers and large vessels are not otherwise abnormal."

Subsequently, it was learned from the mother that although he was ambulatory, the patient had not been as active since the stabbing episode as previously and that he had developed increasing fatigue and shortness of breath.

At operation, a thoracotomy was done and because of considerable hemorrhage encountered it was deemed unwise to continue the procedure. The patient died four hours later.

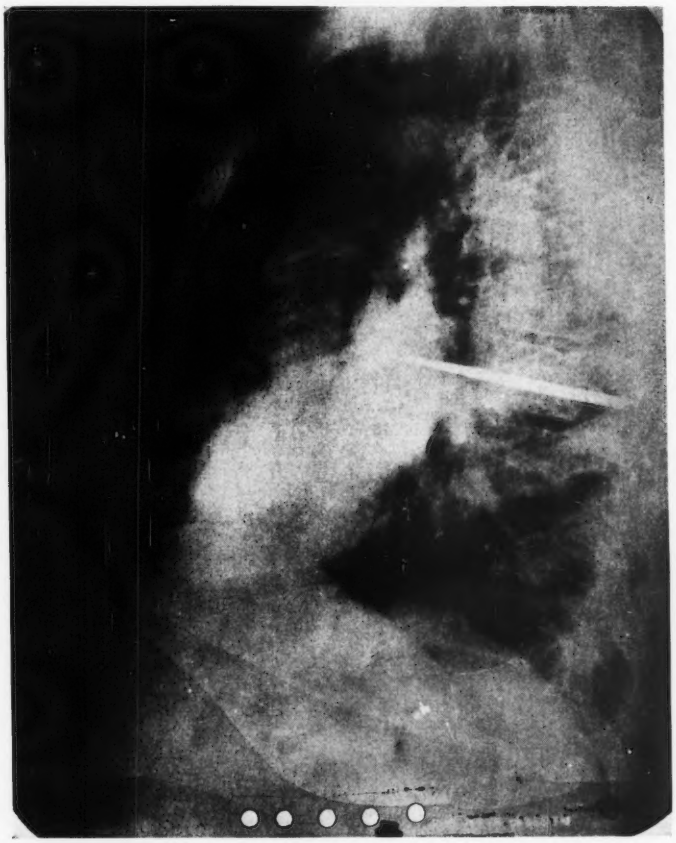

FIG. 3.—Angiocardiogram, showing heart and aorta with ice pick in situ.

Necropsy

Necropsy was performed fifteen hours post mortem. The body was that of a well nourished, well developed Negro, 157.5 cm. (5 ft. 3 in.) tall, scale weight 128 lbs. It was not possible to identify with certainty the scar marking the site of the stab wound which had been inflicted eight months previous. Two small 3 mm. sized pigmented scars were noted, one situated 2.5 cm. to the left and the other just to the right of the midline at about the level of the sixth dorsal vertebra. The pertinent necropsy findings were:

The structures in the peritoneal cavity appeared normal.

The right lung was firmly adherent to the chest wall, posteriorly and laterally, by old fibrous adhesions. The left lung was free and no fluid was found in the left pleural cavity.

The heart (fig. 4) was found free of adhesions in the pericardial sac. The latter was intact and contained only a few cc. of clear fluid. Although the heart was dilated, it was normal in configuration and weight (280 grams). On removal of the heart from the pericardial sac, the track of a small stab wound was found at about the midpoint of the posterior wall of the left aricle. Through a small perforation, 5 mm. in diameter, a broken off ice pick blade projected through the cavity of the auricle,

transfixing it and the anterior leaflet of the mitral valve. The segment of the blade which was imbedded in the heart was 4 cm. in length; the base of the blade, measuring 4.3 cm., was firmly impacted in the left lateral position of the body of the sixth dorsal vertebra but did not enter the spinal canal. On removal of the blade, no evidence of osteomyelitis was found. The weapon was directed forward and slightly medial. The blade, in penetrating the auricle, passed lateral to the aorta and esophagus and did not perforate either of those two structures. There was evidence of a localized injury to the adventitia of the aorta in the form of a small brownish gray scar adjacent to the site of the injury. Examination of the heart revealed two unhealed perforations in the anterior leaflet of the mitral valve, one 9 mm. and the other 12 mm. in length, and each 4 mm. in width and 6 mm. apart. The point of the blade at the end of the track lay in the outflow tract of the left ventricle, just below the level of the undefended space. A slight amount of fibrous thick-

FIG. 4.—Photograph of opened heart, showing ice pick blade projecting from posterior wall of left auricle and punctures and endocarditis of mitral valve.

ening of the endocardium of the septum was noted at this point. In association with the perforations in the mitral valve there was a superimposed vegetative endocarditis in the form of broad masses of gray colored granular vegetations surrounding the two perforations on the auricular aspect of the anterior valve leaflet. The area covered by the vegetations was 4 cm. by 2.5 cm., the longer dimension extending up onto the interauricular septum where the bulk of

the vegetation was found. Only a few small vegetations were noted on the ventricular surface of the perforated valve leaflet. Surrounding the perforation in the posterior wall of the left auricle through which the ice pick blade protruded there was a small mass of friable thrombotic material measuring up to 4 mm. in thickness. The inflammatory process did not involve the posterior valve leaflet. The coronary arteries were not sclerosed and no occlusion of the larger branches could be demonstrated. In order to preserve this unusual specimen, it was thought too valuable to sacrifice the heart for microscopic studies and it was preserved as a museum specimen, and for this reason the coronaries were not completely dissected out. There was a circumscribed but not sharply demarcated zone of fibrosis, grayish white in color, replacing a portion of the myocardium in the posterior wall of the left ventricle, situated just to the left of the posterior interventricular sulcus. On section, this fibrous tissue replacement extended almost completely through the cardiac muscle, its over-all dimensions were 5.5 cm. in length and up to 4 cm. in width. It was evidently the fibrous replacement of an infarction. The remaining valves of the heart were normal and there was no evidence of prior inflammation of the injured mitral valve leaflet.

There was slight fibrous thickening of the areolar tissue of the posterior mediastinum surrounding the position of the impacted ice pick blade. There was no evidence that any phlegmonous posterior mediastinitis had existed.

Examination of the broken off blade following its removal revealed a fairly clean smooth surface and an unbroken sharp pointed blade, 7.8 cm. (3¼ inches) in length, the diameter of the shaft at the broken end being 3.5 mm.

The aorta throughout its length was smooth and elastic.

Both lungs were heavy, congested and edematous and on section were pale.

The liver was normal in size and on section was dry and pale, but the markings were normal; it weighed 1400 grams.

The spleen was not enlarged and was bound down by fibrous adhesions. It weighed 100 grams, was flabby in consistency and contained several large circumscribed anemic infarcts which were yellow in color, firm and depressed. The largest infarct was 2 cm. by 2.5 cm. and up to 9 mm. in depth. The remainder of the splenic pulp was red in color and flabby.

The kidneys together weighed 240 grams and were about normal in size. Numerous, variable sized anemic infarcts, similar to those found in the spleen, were distributed over the surface of each kidney. These infarcts were circumscribed, yellow in color and depressed. They appeared of varying age and were up to 2.5 cm. in diameter. On section they revealed a characteristic wedge shape and exhibited evidence of organization. The uninvolved parenchyma was pale but otherwise presented normal markings. The pelves and ureters were normal.

The bladder contained 60 cc. of pale urine.

All of the other organs in the body appeared normal.

The brain was removed; its surface was pale, the meninges were clear, and the arteries at the base were narrow and delicate. Sections revealed a recent anemic infarct, 6 by 9 mm., in the posterior half of the putamen. Several small areas of swelling and fresh infarction of the cerebral cortex were also found, including one in the left temporal lobe.

In addition to the above, the autopsy revealed evidence of considerable hemorrhage which had occurred during the operative procedure.

Discussion

The symptoms which brought this patient to the hospital were referable to the kidneys. Because of the bizarre murmurs in various anterior and posterior locations, he was fluoroscoped immediately. It was then that the existence of the ice pick was discovered. Our first problem in this case was the exact location and path of the foreign body. The roentgenograms of the chest in the anterior, posterior and right lateral positions placed the anterior end of the pick in the region of the left auricle and suggested that the metallic object was fixed in the body of a dorsal vertebra. Because of the many important structures which are in posterior relation to the left auricle, it was necessary to ascertain whether any of these were also involved. The barium paste revealed the esophagus to be pushed slightly to the right, but did not help in definitely establishing whether there was any injury to the esophagus or aorta. The angiocardiogram indicated the proximity of the aorta to the weapon but did not establish whether that vessel was actually transfixed by it. Furthermore, it seemed unlikely that the aorta could have been perforated and not have resulted in serious hemorrhage.

Here was the unique instance of an ice pick wound of the thorax in which a large foreign body in the form of the blade of an ice pick was fixed within the body of a dorsal vertebra, the point projecting into the left auricle and transfixing the anterior leaflet of the mitral valve. The blade also grazed the left lateral surface of the aorta and esophagus without perforating these structures. Although the wounding had occurred six months before ad-

mission to the hospital, the patient did not complain of precordial pain, dyspnea or palpitation. It is remarkable that the heart maintained its normal rhythm and rate with a fixed metallic object piercing it and transfixing the left auricle and mitral valve.

When the episode of transitory hemiplegia occurred, cerebral embolization from a mural thrombosis of the injured left auricle was considered. Following the cerebral embolism the renal symptoms were presumed to have resulted from embolization from the same source. It was also possible that the left lumbar pain was partly associated with the splenic infarction. During the first two days after admission, the temperature ranged between 100 and 101 F., and thereafter the patient was afebrile except for one morning two months later when the temperature was 101 F. The presence of vegetative endocarditis was not suspected clinically and blood cultures were not taken. Petechiae were never seen.

Reasons for the removal of foreign bodies from the heart as summarized by Harken and Zoll[6] are: (1) to prevent embolism of the foreign body or the development of thrombosis and resultant embolism, (2) to reduce danger of bacterial endocarditis, (3) to prevent recurrent pericardial effusions, (4) to reduce incidence of myocardial damage. Since this patient already had multiple embolization, surgical removal of the offending weapon was deemed wise.

The electrocardiographic changes encountered in traumatic wounds of the heart are in the main due to one or more of the following factors: (1) myocardial damage by the foreign body, (2) pericarditis, (3) injury to an important branch of a coronary artery. Noth[7] has recently published an excellent article on the electrocardiogram in penetrating wounds of the heart; he reviewed the literature and presented 23 cases, some of which had been followed for periods of five to thirty-six months after injury. He stated that the electrocardiographic findings such as those of pericarditis, bundle branch block, or myocardial infarction may be accepted as definite evidences of cardiac involvement, whereas T-wave abnormalities and minor deviations of the RS-T segments cannot be relied upon as criteria of injury since they can also be caused by shock, anemia or displacement of the heart which are often present in thoracic wounds without cardiac involvement. The first electrocardiogram (fig. 2) revealed an elevated S-T_2 with a small Q_3 and deep inversion of T_3. The high voltage of the T and R waves in the precordial leads are reciprocal to a posterior wall infarction. The subsequent tracings indicated a return of the S-T_2 to the base line, inversion of T_2, a deeper Q_3 and a deeper coving of T_3, all of which are progressive changes produced by a posterior wall infarct. In view of the fact that the coronary arteries showed no evident occlusive disease and the presence of other embolic phenomena, it is reasonable to conclude that the myocardial infarct was also embolic in origin. Although the pericardial cavity was traversed when the weapon entered the posterior wall of the left auricle, a pericarditis did not develop beyond the margin of the perforation. The presence of an infarct in the posterior wall of the left ventricle was confirmed at autopsy.

The ice pick could not be seen in the postero-anterior view in the chest x-ray films because in that view only the point was seen. Systolic and diastolic murmurs were heard over the entire precordium and also posteriorly in the interscapular area. The presence of both murmurs was shown on the phonocardiogram. Necropsy revealed that these murmurs were caused by two perforations in the anterior leaflet of the mitral valve. Despite the transfixion and perforations of the larger of its leaflets, the mitral valve continued to function and the patient did not manifest dyspnea or pulmonary congestion and, in fact, had no cardiac complaints.

Summary

An unusual case is reported of survival for eight months following an ice pick stab wound of the back in which the broken off blade remained impacted in the body of the sixth dorsal vertebra and transfixed the left auricle and anterior leaflet of the mitral valve. The disability was caused by the development of a vegetative endocarditis of the injured valve which produced multiple embolization of the

kidneys, spleen and brain. Death occurred following an unsuccessful attempt to remove the weapon surgically. Electrocardiographic studies revealed changes consistent with a posterior wall infarction which was confirmed at necropsy.

ACKNOWLEDGMENT

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Coronary Embolism: Review of the Literature and Report of a Unique Case

By VINCENT MORAGUES, M.D., MALCOLM B. BAWELL, M.D., AND E. LEE SHRADER, M.D.

This is a brief review of the literature on coronary embolism and a case report of a very unique type of coronary embolus—a piece of calcium from a calcified aortic valve. Microscopic sections revealed that the calcium plaque was covered by endothelium which had grown out from the vessel wall, thus attaching it to the coronary artery. The patient lived approximately two months after the embolism occurred.

EMBOLIC occlusion of the coronary arteries is a very rare occurrence, but probably not as rare as the few reports in the literature would lead one to believe. Saphir,[1] in 1932, reviewed 16 cases of coronary embolism from the literature, and reported 3 cases of his own observation. Garvin and Work,[2] in 1932, added 3 cases which had occurred in patients with bacterial endocarditis. Porter and Vaughn,[3] in 1940, reported 3 more cases occurring in patients with syphilitic aortitis associated with mural thrombi of the aortic wall. In 1941, Hamman[4] was able to refer to 40 cases, 30 from the literature and 10 from the records of the Johns Hopkins Hospital. In recent years, individual cases have been reported by Ivanov,[5] Park,[6] Greenstein,[7] Pratt-Thomas,[8] and Ramos[9]; thus there is a total of some 45 cases of coronary embolism referred to in the literature.

From these reports there appear to be six possible sources for emboli which may occlude the coronary arteries[4]: (1) Bacterial vegetations on the mitral or aortic valves (20 cases in the literature). (2) A mural thrombus on an arteriosclerotic or syphilitic lesion in the ascending aorta (10 cases). (3) Intracardiac mural thrombi (5 cases). (4) Thrombi in the peripheral veins (paradoxical embolism) (4 cases). (5) A thrombus or atheromatous material in a coronary artery (2 cases). (6) Thrombi in the pulmonary veins (2 cases).

We present here a case of coronary embolism in which the source of the embolus is unique.

From the Departments of Pathology and Internal Medicine, St. Louis University School of Medicine, St. Louis, Mo.

CASE REPORT

A 43 year old white man was found to have a systolic aortic murmur fifteen years prior to hospitalization. No history of rheumatic fever was elicited. The patient had been in good health except for occasional attacks of precordial pain which had become more severe and had occurred oftener within the last two years. On December 14, 1947, while doing physically laborious work, the patient developed shortness of breath, anginal pain and a feeling of tightness in his chest; dyspnea was so marked that he had to sit up most of the night. The next morning the patient was deeply cyanotic and was coughing up some bloody sputum. He lapsed into unconsciousness in the process of hospitalization. Oxygen, atropin and Metrazol were given, and the patient was digitalized. His condition improved after digitalization and he was discharged after a hospital stay of one week, on a maintenance dose of 0.1 mg. digitoxin.

The patient returned to work and had no complaints, except for a dull ache on the left side of the chest. About February 1, 1948 he developed a sharp precordial pain radiating to his left arm and marked dyspnea; he was rehospitalized.

The patient was tall, slender, malnourished and ashen pale in color. He spoke with great effort because of dyspnea. The apex impulse was in the seventh intercostal space in midaxillary line. The right border of the heart was 4 cm. from mid sternal line in the fifth intercostal space. A mitral systolic murmur and a harsh aortic systolic murmur were heard over the second intercostal space to the right of the sternum transmitted toward the vessels of the neck. A diastolic aortic murmur was also present but heard best in the third intercostal space to the left of the sternum. At times there was a suggestion of a systolic thrill over the aortic area. The pulse was faint and weak, the rhythm was regular, and the pulse rate was 100 per minute. The blood pressure was 90/80 in both arms. There were many moist râles in the lung bases. The liver was palpable 9 cm. below the right costal margin; it was tender and presented a faint pulsation. There was mild clubbing of

the fingers. Laboratory studies were not significant. An electrocardiogram revealed inversion of the T wave in Leads I and II, depression of the S-T segment in Lead I, and elevation of the S-T segment in CF_4. Two previous electrocardiograms taken during January showed essentially the same picture. Radiographic examination of the chest revealed a pronounced enlargement of the cardiac shadow both to the right and to the left. The aortic shadow was very broad and there was calcification in the area of the aortic valve.

Although the patient was irritable and anxious, he improved after being placed at rest and put on a low sodium diet and digitalis. On the twelfth hospital day, while resting in bed talking to his wife, he suddenly became deeply cyanotic and expired.

Pathologic Examination. The body showed cyanosis and enlargement of the superficial veins. All the serous cavities contained fluid transudates.

The heart weighed 760 grams and showed some dilatation of all chambers. The left ventricular myocardium measured 20 mm. in thickness and the right 6 mm. In the anterior wall of the left ventricle, and near the apex of the heart there was an area of infarction about 5 cm. in diameter involving the anterior wall of the left ventricle and a portion of the interventricular septum. Some intraventricular mural thrombi were found attached to the infarcted area. The aortic valve was severely stenosed and distorted by nodular masses of calcium (fig. 1). The coronary ostia were patent and the coronary arteries showed very little atherosclerosis. A small fragment of calcific material 3 mm. long was found occluding the anterior descending branch of the left coronary artery 2.5 cm. from the aortic opening of the vessel (fig. 2).

Both lungs showed moderate congestion and edema, and the lower lobes revealed small hemorrhagic infarcts. The liver weighed 1300 grams, had round margins and was severely congested. No permission was obtained for examination of the head.

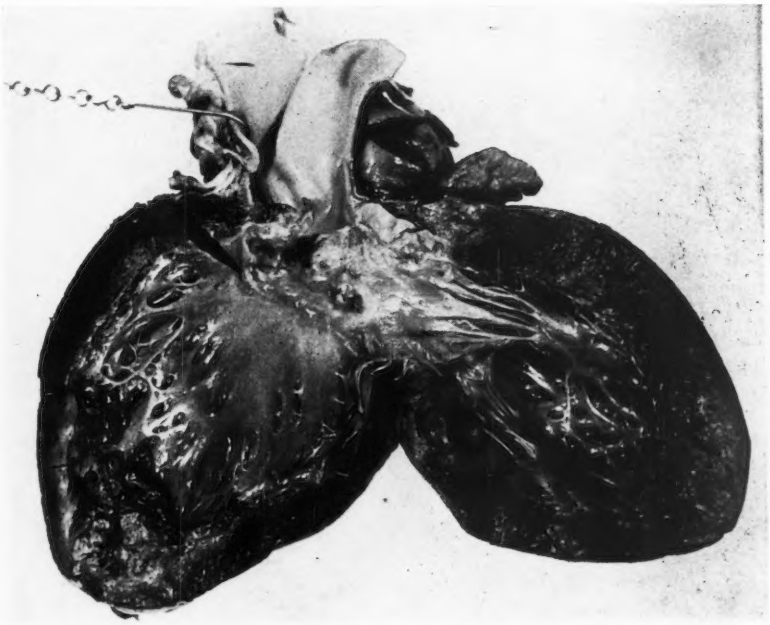

FIG. 1.—Nodular calcification of the aortic valve and the myocardial infarct at the apex with mural thrombosis.

Sections from the area of infarction in the left ventricle revealed the muscle to be largely replaced by granulation tissue infiltrated with chronic inflammatory cells. On the endocardial surface, there were organizing thrombi. The small coronary branches were well preserved and patent. The anterior descending branch of the left coronary artery showed a large mass of amorphous basophilic material attached to the intimal lining of the vessel by several thin pedicles of connective tissue covered by endothelium. The entire calcific mass was also covered by endothelium. The wall of the vessel was well preserved and showed no arteriosclerosis (fig. 3). The

FIG. 2.—Calcific embolus impacted in the anterior descending branch of the left coronary artery.

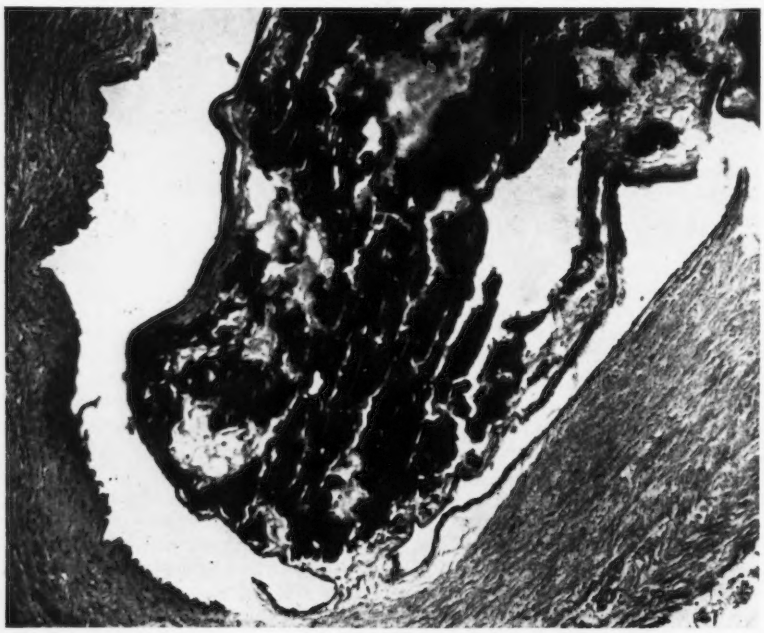

FIG. 3.—Section of the coronary artery at the site of the embolus. Notice the normal arterial wall and the large calcific mass completely relined by vascular endothelium.

aortic valve revealed amorphous masses of basophilic, calcific material. No bacteria were seen. The ascending aorta presented an occasional small accumulation of lipoid material in the intima.

The lungs showed many heart failure cells and areas with much hemorrhage into the alveoli and bronchi. A number of organizing thrombi were seen in the small branches of the pulmonary artery. The liver revealed marked central congestion and necrosis of the central portions of the lobules.

Discussion

It was noted in reviewing the literature that about one half of the cases of coronary embolism were associated with bacterial endocarditis. In such cases the emboli consisted of fragments of vegetations and usually contained bacteria. Saphir[10] reported the presence of myocardial granulomas in 4 cases of subacute bacterial endocarditis which had been treated with antibiotics. These granulomas presented a calcific center, the result of microscopic emboli from healed and calcified vegetations of the aortic valve.

Our case is unique in that the large calcific embolus originated in a nodular, calcified aortic valve without bacterial endocarditis.

We believe that the patient here presented suffered an acute embolic coronary occlusion in December 1947. The date of this accident is confirmed by the clinical history.

The amount of organization and fibrosis of the infarcted area of the myocardium and the complete attachment of the embolus by a covering of endothelium to the vessel wall would substantiate the fact that the accident occurred several months prior to death. The rigidity and irregular shape of this calcific embolus would not permit a complete occlusion of the vessel even though the embolus was firmly impacted in the artery. These conditions would permit some blood flow through the involved vessel. This fact, we believe, accounts for the survival of this patient at the time of the initial acute embolic accident.

Summary

The literature on coronary embolism is reviewed. The findings in an additional case are reported. This case is somewhat unique in that the source of the embolus was a calcific mass which became detached from a calcified aortic valve.

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Atypical Secondary or Symptomatic Thrombocytopenic Purpura Developing with the Use of Quinidine Sulfate

By DONALD C. COLLINS, M.D.

Quinidine sulfate, which has a very similar chemical structural formula to that of quinine bisulfate, may on a rare occasion be the etiologic causative agent of an atypical secondary or symptomatic thrombocytopenic purpura of serious degree. Fortunately, the withdrawal of the drug results in a rapid return to normal of the hematologic picture. A case report of such an occurrence is presented. Three additional case reports have been collected from the literature since 1941.

ATYPICAL secondary or symptomatic thrombocytopenic purpura has been reported to develop occasionally following the ingestion of certain chemicals acting as bone marrow poisons. Some of the most common offending agents include benzol, nitrogen mustards, gold salts, Sedormid, bismuth, dinitrophenol, iodides, sulfonamides, arsenicals, phenobarbital, ergot, and quinine.[1, 3, 4, 6, 8, 9] Recently a study has been undertaken by the Department of Pharmacology and Toxicology of the University of Rochester School of Medicine and Dentistry[2] to determine to what extent therapeutic drugs and exposure to toxic chemicals may contribute to increased mortality and disability due to accidents. This study is a step in the right direction to publicize the possible deleterious effects that may follow the use of specific drugs or chemicals.

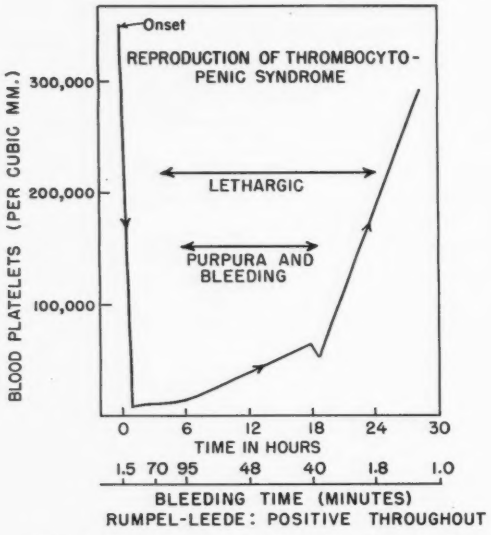

FIG. 1. Reproduction of Thrombocytopenic Syndrome by the Ingestion of 0.2 Gm. of Quinidine Sulfate.

The present article represents the fourth report of purpura developing following the oral administration of quinidine sulfate to a patient with cardiac disease. Table 1 summarizes the essential data in this case as well as those of the cases reported previously.[1, 5, 7] An atypical secondary thrombocytopenic purpura was manifest in my patient following the use of a relatively small amount of quinidine sulfate in the treatment of auricular fibrillation. One week after recovery from the initial attack of purpura this patient was given a small test dose (0.2 Gm.) of the drug. Figure 1 graphically demonstrates the reaction. The spectacular rapid drop in the number of blood platelets in the circulating blood to 1,000 per cu. mm. one hour after the oral administration of the drug together with the fact that it required nearly twenty-four hours for the patient to recover from the severe effects of the thrombocytopenic syndrome is a grave warning that caution must be employed in the indiscriminate use of quinidine sulfate and that physicians must be on their guard when employing this valuable therapeutic agent.

Pirk and Engelberg[3] called attention to the fact that quinine bisulfate rather frequently may cause an atypical toxic thrombocytopenic purpura. Howard[3] in his recent publication presents the chemical structural formulas of

TABLE I.—*Data on Reported Cases of Atypical Secondary or Symptomatic Thrombocytopenic Purpura Occurring with the Use of Quinidine Sulfate*

Data	Author and Year			
	Brock, O. J., 1941[1]	Nudelman, P. L. et al., 1948[7]	Larimer, R. C., 1949[5]	Collins, D. C., 1950
Sex and Age in Years.	Female, 27.	Female, 57.	Female, 35.	Female, 76.
Occupation.	—	Seamstress.	Housewife.	Widow.
Nationality.	Norwegian.	Italian.	Canadian.	American.
Past History of Bruising Easily.	No.	—	Yes.	No.
Serious Childhood Diseases.	—	Tuberculosis of bone.	Scarlet fever.	Rheumatic fever; severe rheumatoid polyarticular arthritis.
Cardiac Disease.	Extrasystoles; Auric. fibrillation.	Supraventricular tachycardia; hypertensive and rheumatic heart disease.	Thyrotoxic heart disease; auric. fibrillation; alternating ventric. extrasystoles; arterial hypertension.	Hypertensive and rheumatic heart disease; auric. fibrillation, rate 360; mitral insuffic.; coronary thrombosis.
Blood Pressure and Pulse.	—	150/60; 88.	160/110; 80.	188/124; 96-180.
Previous Operations.	—	—	Thyroidectomy (1932).	Fracture rt. tibia at knee (1939).
Days Duration of Present Illness before Quinidine Sulfate Was Started.	14.	14.	5.	One-half day.
Electrocardiogram.	—	—	Rate 80, alternating ventricular extra systoles.	Auric. fibrillation; rate 360; arterial sclerosis; L.V.D.
Total Dosage of Quinidine Sulfate before Onset of Purpura.	8.0 Gm.	6.0 Gm. in 11 days.	8.0 Gm. in 5 days.	7.2 Gm. in 5 days.
Widespread Purpura; Gingival and Nose Bleeding.	Yes.	Yes.	Yes.	Yes.
Vaginal Bleeding.	?	?	Moderate.	No.
Red Blood Count.	5,460,000	4,700,000	4,900,000	3,840,000
White Blood Count.	8,400	8,300	8,300	11,600
Differential Count.	Normal.	Normal.	88% neutrophils, 11% lymphocytes, 1% eosinophils.	82% neutrophils, 10% lymphocytes, 4% monocytes, 2% eosinophils, 2% basophils.
Sedimentation Rate.	—	—	22 mm. hour, cor.	18 mm. hour.
Blood Platelets.	23,000 per cu. mm.	4,000 per cu. mm.	None seen.	6,000 per cu. mm.
Bleeding Time.	8½ min.	30 min.	6 min.	20 min.
Coagulation Time.	1¾ min.	7 min.	9½ min.	7 min.
Clot Retraction.	—	None in 3 hours.	—	None in 2 hours.
Prothrombin Time.	—	Normal.	17 sec.	Normal.
Rumpel-Leede Test.	—	Positive.	Positive.	Positive.
Sternal Marrow Aspiration.	Normal.	Normal.	—	Reduced megakaryocytes.
Treatment.	Quinidine sulfate stopped.	500 cc., citrated blood transfusion; quinidine sulfate stopped.	Vitamins C & K, and rutin; quinidine sulfate stopped.	Vitamins C & K, and rutin; quinidine sulfate stopped.
Method of Reproducing the Clinical and Hematologic Picture of an Atypical Secondary Thrombocytopenic Purpura.	0.4 Gm. quinidine sulfate, "several times."	On fourth day by 0.1 Gm. quinidine sulfate by mouth.	On ninth day by 0.15 Gm. quinidine sulfate by mouth.	On seventh day by 0.2 Gm. quinidine sulfate by mouth.

both quinidine sulfate and quinine bisulfate. Since formulas of these two substances are quite similar, it is not surprising to find instances in which quinidine sulfate may cause a purpuric reaction similar to that caused by quinine bisulfate.

Summary

The fourth reported instance of an atypical secondary severe thrombocytopenic purpura resulting from the oral ingestion of 7.2 Gm. of quinidine sulfate over a five-day period is recorded. One week following recovery a second severe atypical thrombocytopenic syndrome was produced in the patient by the oral administration of 0.2 Gm. of this drug. This brief report is made in the hope that physicians will remember that quinidine sulfate, like its more notorious "cousin," quinine bisulfate,[3, 8] can cause a severe, alarming, atypical secondary thrombocytopenic purpura, which, if the etiologic factor is unrecognized, may result in the death of the patient.

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Primary Systemic Amyloidosis Mimicking Chronic Constrictive Pericardial Disease

By William T. Couter, M.D. and Rudolph E. Reichert Jr., M.D

The characteristically altered physiologic pattern in chronic constrictive pericarditis is the resultant of the diminished cardiac expansibility. A widespread infiltrative myocardial disease in which cardiac expansibility was equally limited should simulate the former entity very closely. This extremely rare entity is illustrated in this case report.

PRIMARY amyloidosis is a rare disease; less than 60 cases have been reported to date.[1] Lindsay[2] surveyed the cardiac complications of 45 cases of primary amyloidosis and found that 39 had cardiac amyloid deposition and that 23 had signs of congestive failure. He believed that in some, the extensive amyloid deposition might have interfered greatly with the normal range of cardiac contraction and relaxation but none of the 45 cases were reported as simulating chronic constrictive pericarditis.

Chronic constrictive pericarditis is a relatively common disease. It is usually recognized late in its course after the reduced cardiac output has resulted in a pathognomonic physiologic complex. In this entity, the restriction of cardiac movement is caused by a thickened and sometimes calcified pericardium that may or may not be associated with a collection of pericardial fluid. A generalized myocardial disease would be capable of producing an identical symptom complex if the disease process could produce significant restriction of cardiac contraction and relaxation.

The stimulation of chronic constrictive pericardial disease by a generalized infiltrative myocardial disease is extremely rare; only one other case has been reported.[3] In the case report to be presented all of the classic symptoms and clinical signs of constrictive pericarditis were superimposed upon the clinical manifestations of primary systemic amyloidosis.

From the Department of Internal Medicine, The Medical School, University of Michigan, Ann Arbor, Michigan.

Case Report

The patient was a 38 year old white housewife, whose general health had been good prior to September 1948. Two pregnancies fourteen and eight years previously had been without untoward incident. In September 1948 she developed a "cold," characterized by excessive lacrimation, rhinorrhea, and headache. Approximately one week later she noted the onset of a pressing pain over the lower sternum synchronous with her heartbeat and intensified by exercise. This discomfort persisted continuously for one month and then shifted to the lower abdomen where it was augmented after eating.

She was admitted to a neighboring hospital November 21, 1948 complaining chiefly of fatigue, anorexia, and abdominal pain. In addition, ecchymoses had appeared in the soft tissues around the right eye without antecedent trauma. The remainder of the history was noncontributory. Significant physical findings were a blood pressure of 110/68, a persistent tachycardia of 130 per minute at bed rest, pallor, a small ecchymotic area around the right eye, and a few small petechiae under the tip of the tongue. Laboratory values were normal for the following procedures: reticulocyte and blood platelet count, bleeding, clotting, and clot retraction time, hematocrit, blood glucose, blood nonprotein nitrogen, serum albumen, globulin, potassium, and sodium, urea clearance, basal metabolic rate, thymol turbidity and flocculation, cephalin-cholesterol flocculation, and repeated blood cultures. A Rumpel-Leede test was normal. X-ray examination of the upper gastrointestinal tract, kidneys, and colon as well as gastric analysis and biliary drainage were normal. The hemoglobin was 13.3 Gm. per 100 cc. and the erythrocyte count 3,940,000 per cubic millimeter. The leukocyte count was 11,700 per cu. mm., with a normal differential leukocyte count. The sternal marrow was moderately hypoplastic. A urinalysis was normal with the exception of a plus 3 proteinuria without Bence-Jones proteinuria. The stool showed a plus 4 guaiac reaction. There was 10 per cent retention of bromsulfalein at 45 minutes following the injection of 5 mg. per kilogram of body weight. The electrocardiogram revealed small complexes in Leads I, II and III with inversion of the T waves in Leads

II and III. The patient remained afebrile during her three weeks' hospitalization and was treated symptomtaically.

Following discharge she continued to do poorly although her abdominal discomfort decreased somewhat in intensity. In January 1949 she was again hospitalized because of the passage of "one pint of fresh blood" from the rectum. Physical examination at this time revealed that ecchymoses of the buccal mucous membranes had appeared, the liver edge was palpable for the first time, and the reclining

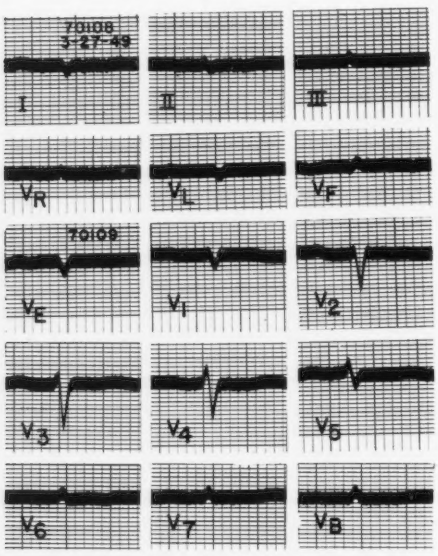

FIG. 1.—Standard limb leads, unipolar limb leads, and unipolar precordial electrocardiographic leads showing the uniformly small QRS complexes and flat T waves in all leads.

blood pressure was 82/52. The admission hemoglobin was 10.6 Gm. per 100 cubic centimeters. The leukocyte count was 6850 with a normal differential. Repeated determinations of the blood nonprotein nitrogen, and serum potassium, sodium, albumen, and globulin were normal. A Kepler water balance test was negative. A plus 4 guaiac reaction was again present in the stool. X-ray examination of the skull, colon, and chest was normal. Proteinuria persisted and the retention of bromsulfalein had risen to 22 per cent at the end of 45 minutes. The sternal marrow was hypoplastic with a shift of the myeloid-erythroid ratios from an initial 6:1 to 11:1. She was discharged after two blood transfusions and symptomatic therapy which was followed by gradual improvement although the hypotension and the tachycardia persisted.

In February 1949 she first noted oliguria and dependent edema and was admitted to the neighboring hospital for the third time on March 23, 1949. She appeared severely ill, was pale, and showed evidence of recent weight loss. The reclining blood pressure was 60/45 in the upper extremities and unobtainable in the lower; she complained of dizziness and lightheadedness in the upright position. Marked dependent edema was present and the liver edge was palpable at the level of the umbilicus. Proteinuria was again present; the microscopic examination of the urine revealed many leukocytes and a few erythrocytes per high power field with many fine granular casts per low power field. The hemoglobin was 11.8 Gm., the erythrocyte count 4,380,000, and the leukocyte count 6800.

She was admitted to the University Hospital March 26, 1949, approximately seven months after the onset of the first symptoms. Physical findings were as those previously described. The reclining blood pressure was 80/60, and the pulse rate 108 per minute with a significant pulsus paradoxus. The facies was mask-like with some peri-orbital edema. The neck and other peripheral veins were markedly distended; sacral and peripheral edema of the lower extremities as well as signs of bilateral pleural effusion were present. A tender liver edge was palpable 10 cm. below the right costal margin. The left border of cardiac dulness was at the mid-clavicular line in the fifth intercostal space. The heart sounds were distant and regular. A prominent third sound was present in early diastole at the apex.

Bleeding, clotting, and clot-retraction time, prothrombin concentration, direct and indirect bilirubin, hemoglobin, erythrocyte and leukocyte counts, and the differential leukocyte count were normal. Urinalysis showed proteinuria and cylindruria and urine cultures grew *Staphylococcus aureus* and a nonhemolytic streptococcus. The urea clearance was 64 per cent at the first hour and 59 per cent at the second. The blood urea nitrogen was 28.6 mg. per 100 cc. with an initial nonprotein nitrogen of 37 mg. per 100 cc.; this latter value subsequently rose to 82 mg. per 100 cc. The total serum proteins were 5.8 Gm. per 100 cc. with albumen 2.4 Gm. and globulin 3.4 Gm. per 100 cc. The cephalin-cholesterol flocculation test was negative at 24 and plus 3 at 48 hours. There was 32 per cent retention of bromsulfalein at 45 minutes (5 mg. per kilogram). Blood creatinine was 1.4 mg. per 100 cc. The arm-to-tongue circulation time was 35 seconds (normal 18 seconds). An old tuberculin series was negative for dilutions of 1/10,000 and 1/1000 and the Kahn serologic test was negative. Venous pressure in the right arm was 268 mm. of water. Electrocardiograms with standard limb leads, unipolar limb leads, and unipolar precordial leads were not remarkable except for the small QRS complexes and the flat T waves in all leads (fig. 1). Fluoroscopy demonstrated the heart to be of normal size; no pulsations of the cardiac silhouette could be definitely identified.

In view of the clinical and laboratory findings associated with the syndrome of constrictive peri-

cardiac disease and the history of a hemorrhagic tendency, the possibility of a partially organized hemorrhagic pericardial effusion was considered and a diagnostic pericardial tap performed. Eighty-five cc. of rapidly clotting serosanguinous fluid was easily obtained and 50 cc. of air replaced. An x-ray film of the chest demonstrated the presence of additional significant pericardial fluid. Examination of the aspirated pericardial fluid failed to demonstrate acid-fast or other bacteria or neoplastic elements.

In spite of supportive therapy, the anasarca increased, periods of mental confusion became more frequent, and a shock-like state consistently occurred when the patient assumed the sitting position. In view of the possibility of some type of restricting cardiac disease an exploratory thoracotomy was performed April 4, 1949. During that procedure 275 cc. of serosanguinous fluid was removed from the pericardial sac. However, the pericardium itself appeared grossly normal. The right auricular appendage was distended, bluish, and definitely indurated. A partial pericardectomy was performed and the pericardial space left in free communication with the left pleural cavity. Venous pressures were 240 mm. H_2O immediately before and after the operation and 300 mm. during the operation. On the second postoperative day the venous pressure was 300 mm. of water. Post-operatively her condition remained poor and death ensued on the eleventh hospital day.

Postmortem examination.—Autopsy with the exception of the head was performed six and one-half hours after death. The abdominal cavity contained 200 cc. of a straw-colored fluid; there were 700 cc. of a similar fluid in the right and 400 cc. in the left pleural cavity. The heart weighed 430 grams. The remaining pericardium was somewhat thickened but smooth. The epicardial surface underlying the surgical defect was slightly granular and greyish purple. The left ventricular wall measured 17 mm. and the right 4 mm. in thickness. The right auricle was markedly dilated; the left ventricle was also dilated to a moderate degree. An old thrombus was present in the right auricular appendage. The heart valves were normal. The right lung weighed 500 grams and the left 450 grams. The pleural surfaces were smooth. Cut sections of the lung revealed considerable edema fluid. There was slight congestion in the small intestine. The pancreas weighed 100 grams. The liver weighed 2060 grams. The right adrenal gland weighed 11 and the left 14 grams. The right kidney weighed 210 and the left 260 grams. A left paraovarian cyst was present.

Sections were stained with methyl violet in addition to the usual stains. There was massive amyloid deposition in all organs with predilection of involvement of the walls of the small and medium-sized blood vessels.

In the heart there was acute fibrinous epicarditis with serous atrophy of the sub-epicardial fat and sub-epicardial hemorrhage. The nerves and blood vessels in the subepicardium revealed considerable amyloidosis, which in the blood vessels was deposited outside the endothelium. A few amyloid deposits in the adipose tissue did not appear to be related to blood vessels. Throughout the myocardium every muscle fiber appeared to be surrounded by amyloid material (fig. 2) with both atrophy and hypertrophy of the myocardial fibers. In addition there were manifold areas of necrobiosis with karyorrhexis, karyolysis, and vacuolation. Beneath the epicardium in the walls of the small to medium-sized blood vessels and in the substance of the cardiac valves were larger irregular hyalin masses. In some cases the hyalin material was located only in the media of the arteries. These larger masses of hyalin material and the smaller masses in the blood vessels gave a poor metachromatic reaction when stained with methyl violet. The right auricular appendage contained a large recent bland thrombus showing focal areas of beginning autolytic softening and organization. The nerve trunks and ganglia adjacent to the aorta contained amyloid deposition.

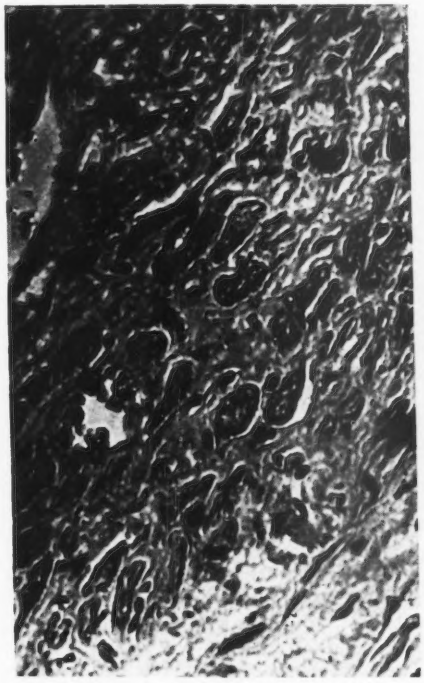

FIG. 2.—Section of the myocardium showing extensive involvement with amyloid with unit encasement of the individual fibers.

Discussion

In this case of primary systemic amyloidosis all of the clinical signs and symptoms of chronic constrictive pericarditis were present. The heart size was within normal limits, although the venous pressure on all occasions was over 250 mm. of water. Small QRS complexes and flat T waves were present in all electrocardiographic leads. No murmurs were audible and the heart sounds were quiet and regular. A prominent apical third heart sound was present in early diastole. The circulation time was prolonged. The systolic blood pressure ranged from 60 to 80 mm. Hg with a small pulse pressure. A persistent tachycardia and a significant pulsus paradoxus were present. The patient was not orthopneic although ascites, dependent edema, and bilateral hydrothorax were prominent.

It is unlikely that cardiac tamponade was a factor in the progressive cardiac embarrassment demonstrated in this case for the venous pressure remained elevated following the removal of all possible constricting structures. The myocardium was widely infiltrated with amyloid to the extent that all the individual fibers were encased in the material. The myocardium had lost its capacity for contraction and relaxation to the degree that cardiac diastole and systole were so restricted that the syndrome of chronic constrictive pericarditis was simulated physiologically.

Summary

A case is reported of primary amyloidosis with extensive myocardial deposition and simulation of chronic constrictive pericarditis.

Acknowledgments

We are indebted to Dr. Raymond Monte of Detroit for the information relative to the patient prior to hospitalization at the University Hospital and to Dr. J. Marion Bryant of Ann Arbor for his many helpful suggestions.

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ABSTRACTS

BLOOD COAGULATION

Lewis, D. W., Munro, F. L., and Munro, M. P.: Prothrombin determinations in dicumarolized patients: a comparison of the one-stage and bedside methods. J. Lab. & Clin. Med. **35:** 16 (Jan.), 1950.

Using a stable thromboplastin, the authors found a close relationship between results obtained by the bedside test and those obtained by the Quick one-stage method. One hundred and eighty-two paired prothrombin determinations were performed by both methods in 16 patients undergoing dicumarol therapy and in 38 normal controls. When the thromboplastin was diluted to give a bedside prothrombin time of 24 to 43 seconds for normal persons, it was found that the clotting powers as derived from the bedside tests were in agreement with those obtained by the use of the more active thromboplastin.

The authors suggest that with the use of a stable, active thromboplastin the bedside test is adequate for the control of dicumarol therapy. It is essential to obtain frequent values on normal blood to ensure that the thromboplastin retains its activity. In order to convert prothrombin times, as obtained by the bedside test, to prothrombin activity, the authors recommend the preparation of a dilution curve by the one-stage method at weekly intervals, or more frequently if the values show any tendency to vary.

MINTZ

Stefanini, M., and Crosby, W. H.: Complementary correction of the defective coagulation mechanism of hemophilic and thrombocytopenic blood. Proc. Soc. Exper. Biol. & Med. **73:** 301 (Feb.), 1950.

The authors found that in both hemophilic and thrombocytopenic blood the defect of the clotting mechanism is due to a lack of active thromboplastin. The addition of thrombocytopenic blood to hemophilic blood results in a mixture in which the clotting time, clot retraction, prothrombin activity and "accelerator effect" of serum all become normal. These findings support the theory that at least two factors are necessary for the formation of active thromboplastin: a plasmatic agent, deficient in hemophilia, and a platelet factor, deficient in thrombocytopenic purpura.

MINTZ

Toohey, M.: Prothrombin estimation and dicoumarol therapy. Brit. M. J. No. 4652: 518 (March 4), 1950.

The author feels that present methods which use dried extract of rabbit brain or Russel-viper venom for prothrombin estimations are impractical or unreliable. With the former a skilled technician is essential, while with the latter false low clotting times may lead to overdosage of anticoagulants, particularly dicumarol. He emphasizes age as a factor in dicumarol susceptibility and advises small doses of the drug in the aged. He feels that it is best to give this drug in small daily doses after initial heavier dosage.

For prothrombin estimation the author recommends a simple thromboplastin preparation made by emulsifying human brain with normal saline to which is added 0.5 per cent phenol as a preservative. The preparation will give a prothrombin clotting time with normal plasma of 13 to 16 seconds. For effective dicumarol therapy a prothrombin clotting time of from 30 to 50 seconds should be maintained with this preparation.

TANDOWSKY

Stefanini, M., and Pisciotta, A. V.: Rate of disappearance of prothrombin from the circulation. Science **111:** 364 (April 7), 1950.

Five rabbits received dicumarol in gum acacia suspension by intubation. After five days prothrombin level was usually lower than 5 per cent of normal, and the concentration of the "labile factor" appeared to be normal or slightly decreased. Prothrombin concentrate obtained from fresh oxalated rabbit plasma was then given intravenously; no reaction or untoward effect was noted. The prothrombin time was then determined in centrifuged plasma at periodic intervals. During this phase of the experiment rabbits continued to receive dicumarol to prevent prothrombin formation by the liver. Using the one-stage Quick method of prothrombin time determination and checking this method by determining the concentration of prothrombin, the authors found that restoration of the prothrombin level to almost 100 per cent of normal immediately followed the injection of the prothrombin concentrate. About 50 per cent of the prothrombin disappeared from the circulation within the first 12 hours, and about 80 per cent in 24 hours. The original level was reached in from 48 to 60 hours.

The authors conclude that prothrombin is promptly utilized or metabolized in the body, and that the concentrate of prothrombin prepared with

the technic described is capable of restoring the prothrombin concentration of dicumarolized rabbits to normal.

WAIFE

CONGENITAL ANOMALIES

Jouve, A., and Pierron, J.: Practical points of electrocardiography in the diagnosis of congenital heart disease. Arch. d. mal. du coeur **42:** 689 (July), 1949.

A specific diagnosis of a congenital malformation of the heart can be made from the electrocardiogram in cases of situs inversus or in cases with an abnormal origin of the left coronary artery from the pulmonary artery. Left axis deviation in a cyanotic child suggests tricuspid atresia. A marked right axis deviation without cyanosis suggests an anomaly of the venous return to the heart. Abnormally tall and notched P waves in all three limb leads can be found in interatrial septal defects. The large diphasic QS pattern is not absolutely characteristic of the presence of a congenital lesion. More suggestive is an axis deviation of +130° in an infant and of +120° in a child. The diagnosis of a congenital heart block may be missed in an infant due to the more rapid rate of the idioventricular pacemaker. A paroxysmal tachycardia is surely of congenital origin only if registered on the fetus in utero or within the first months of life. Auricular flutter with 1:1 conduction may imitate paroxysmal tachycardia in a child. If one finds unexpected electrocardiographic patterns, such as marked right axis deviation in the presence of a patent ductus arteriosus or the absence of marked right axis deviation in a case of Fallot's tetralogy, the patient should be carefully examined for additional lesions before being recommended for operation.

PICK

Boldrey, E., and Nuller, E. R.: Arteriovenous fistula (aneurysm) of the great cerebral vein (of Galen) and the circle of Willis. Report on two patients treated by ligation. Arch. Neurol. & Psychiat. **62:** 778 (Dec.), 1949.

Arteriovenous fistula (aneurysm) connecting the great cerebral vein of Galen and the circle of Willis is a congenital anomaly, apparently of rare occurrence and a pathologic curiosity. This paper presents 2 living patients in whom this anomaly was discovered by means of cerebral angiography. The anomaly may be suspected clinically when there is vascular engorgement of the vessels of the scalp in the presence of a pronounced and persisting bruit. Angiography is then justified for verification. Other findings which are more diagnostic of this condition are a calcified pineal gland, associated enlargement of the head, and a subarachnoid hemorrhage. If the lesion is approached early, before massive venous tributaries have developed, the arteriovenous aneurysm may be successfully ligated.

LECKS

Adams, F. H., Labree, J., and Stauffer, H. M.: Right heart catheterization of the aorta through a patent ductus arteriosus. Pediatrics **5:** 390 (March), 1950.

The authors report 3 cases of patent ductus arteriosus with atypical findings. In these patients, during right heart catheterization, the catheter was inadvertently passed through the patent ductus and down the aorta, thus making a direct and definitive diagnosis. When catheterization of the aorta through the ductus arteriosus is performed, it is possible to catheterize some of the branches of the aorta.

MARGOLIES

Bahnson, H. T., and Blalock, A.: Aortic vascular rings encountered in the surgical treatment of congenital pulmonic stenosis. Ann. Surg. **131:** 356 (March), 1950.

The authors describe variations of a vascular ring due to anomalies of the aortic arch encountered in the surgical treatment of patients with congenital pulmonic stenosis. The diagnosis of a retro-esophageal artery can usually be made by roentgenography with barium swallow. The anomalous vessel causes an abnormal indentation in the posterior wall of the esophagus seen in the customary oblique and lateral projections. It is important to recognize the presence of a retro-esophageal subclavian artery at the time of operation for pulmonic stenosis and appreciate that it may be used in creating an artificial ductus arteriosus. Angiocardiography may demonstrate the anomalous vessel but this diagnostic aid is generally of little help. It has been of great value in demonstrating the side of the aortic arch in several unusual patients.

Three cases of double aortic arch are described. Marked respiratory difficulty as a result of tracheal constriction was present in only one of these patients and was corrected by division of the smaller of the two arches.

KLOSK

Conklin, W. S., and Watkins, E., Jr.: Use of the Potts-Smith-Gibson clamp for division of patent ductus arteriosus. J. Thoracic Surg. **19:** 361 (March), 1950.

The authors describe a technic for using the Potts-Smith-Gibson clamp in dividing a patent ductus arteriosus. The clamp used is one-third larger than the standard clamp devised by Potts. The aorta is exposed by subpleural dissection and the segment opposite the ductus is mobilized. The Potts clamp is then placed around the aortic end of the ductus. The pulmonic end of the ductus is ligated and transfixed and the ductus divided between the pulmonic ligature and the aortic clamp. The latter is then

elevated and rotated to present the divided end of the duct which is repaired with a continuous horizontal mattress suture, approximating intima to intima.

This method of closure has been used on 21 patients with only one death as a result of hemorrhage. The death resulted from faulty technic and a Potts clamp of insufficient size.

The authors enumerate the advantages of the Potts-Smith clamp for division of the patent ductus: (1) Mobilization of the aorta allows more freedom in the development of deep tissue planes about the ductus and in freeing the fibrous bands attached to the posterior wall of the ductus. (2) The aorta is mobilized for temporary clamping in case of hemorrhage. (3) By applying the clamp, dissection of the ductus can be complete without danger of spontaneous rupture from full aortic pressure should the walls of the duct be damaged by aneurysm or subacute bacterial endocarditis. (4) Temporary clamping while the dissection is being completed allows considerable time for the development of latent cyanosis should an unsuspected pulmonic stenosis complicate the ductus.

KLOSK

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Dock, W.: The cause of arteriosclerosis. Bull. N. Y. Acad. Med. **26:** 182 (March), 1950.

Local degeneration and injury are not important in the deposition of cholesterol in skin or intima of blood vessels. Mechanical factors such as constant motion of parts (e.g., anterior mitral leaflet, epicardial parts of the coronary arteries) seem more important in atheroma formation. Other causes include thickness of intima, the level of arterial pressure in both the systemic and pulmonic circuits, dietary fat, and protein and caloric content in those persons whose plasma cholesterol behaves more like that of the rabbit than that of the dog. Of all of the causes of atherosclerosis, the only one easily susceptible to control is myxedema.

WHITE

ELECTROCARIOGRAPHY

Schaefer, H.: A concept of an exact theory of the electrocardiogram. Arch. f. Kreislaufforsch. **15:** 173 (Sept.), 1949.

By measurements of potential differences in a few myocardial fibers on the surface of the exposed dog's heart, the author was able to demonstrate that the length of the initial excitation wave in a single fiber is less than 1 mm. From this he concludes that during the inscription of QRS the single fibers react independently. The regression of the excitation, however, represented by the T wave, occurs slowly and extends over the whole heart and cannot, therefore, be due to the summation of the reactions of individual fibers.

The potentials developed in the extremity electrocardiogram are the result of millions of components represented by vectors created on the epicardial surface. The resultant vector of QRS depends on the order in which the single fibers are activated by the conduction system. Most important in this respect are the relative delay, the direction and the length of the excitation wave in the individual muscle element. Hypertrophy may prolong the QRS duration by elongation of the fibers. The T vector, on the other hand, depends on the time relationship of the regression of excitation in the syncitium of large parts of the heart. The components of the T vector have the direction of the syncitial bridges connecting single muscle fibers.

The excitation wave leaves the conduction system and enters the myocardium in the center of the heart. This point is termed by the author the source (*Quellpunkt*) of the excitation. The further spread of the excitation over the surface of the heart occurs in all directions and many of the vectors of opposite direction equalize each other. This explains the physiologic low voltage of the manifest action currents of the heart. Electrocardiographic preponderance of one side of the heart is produced by unilateral increase of the magnitude of component vectors.

The authors develop a hypothesis which explains the longer persistence of the excitation at the bases by a faster regression of the contraction wave at the apex, the latter giving rise to a kind of peristaltic movement of the heart.

PICK

Masini, V., Biocca, P., and Sposito, M.: The cause of the electrocardiographic changes in acute cor pulmonale. Cuore e circolaz. **33:** 275 (Oct.), 1949.

The cause of the electrocardiographic changes in acute cor pulmonale was studied by a series of experiments in dogs and by clinical observations during pneumonectomy in human subjects. The electrocardiographic changes are attributed by the authors both to right ventricular enlargement and to coronary ischemia. The latter seems to follow arterial hypotension. The changes in the electrocardiogram are considered, therefore, as purely hemodynamic and not the result of pulmonocoronary or pulmonopulmonary reflexes. In dogs, only subtotal occlusion of the pulmonary artery was followed by changes of the electrocardiogram. In man, after pneumonectomy, in spite of a sudden occlusion of the pulmonary artery, the authors never recorded electrocardiographic changes similar to those of acute cor pulmonale.

LUISADA

Meyer, P., and Schmidt, C.: Post-extrasystolic disturbances of repolarization. Arch. d. mal. du coeur **42:** 1175 (Dec.), 1949.

Following premature beats, changes of the T wave may occur. These have been found in 15 per cent of the cases, especially after ventricular premature contractions, and consist of deepening of an inverted T wave or inversion of a usually normal T. These changes may occur only in the chest leads and may be accompanied by increased duration of Q-T. This syndrome, called postextrasystolic T wave changes, is compared to the post-tachycardia syndrome.

LUISADA

Bierman, H. R., Randolph, E., and Sokolow, M.: Effect of toxic doses of 4,4-diamidino-stilbene (stilbamidine) on the electrocardiogram in mice. Proc. Soc. Exper. Biol. & Med. **73:** 210 (Feb.), 1950.

Stilbamidine administered intraperitoneally to mice in doses of 2.5 mg. produced transient and minor electrocardiographic changes. Doses above 5 mg. were lethal. Striking electrocardiographic abnormalities followed by cessation of respiratory and cardiac activity occurred with 4 to 20 mg. Respirations usually stopped within four to six and one-half minutes and cardiac action ceased about eighteen minutes after the injection. The electrocardiographic findings were progressive, varying degrees of sino-auricular, auriculoventricular and intraventricular block eventuating in death. There were no significant ST-T changes.

The constancy and reproducibility of the electrocardiogram in the normal mouse indicates that the effect of drugs upon the electrocardiogram may profitably be studied in this animal.

MINTZ

Wener, J., Scherlis, L., Sandberg, A. A., Master, A. M., and Grishman, A.: Study of RS-T segment changes in induced coronary insufficiency using esophageal leads. Preliminary report. J. Mt. Sinai Hosp. **16:** 400 (Mar.–Apr.), 1950.

Simultaneous esophageal, standard and unipolar extremity and precordial lead electrocardiograms were recorded in patients with angina pectoris, before and immediately after the two-step exercise test. Immediately after exercise, in the esophageal leads taken at atrial levels, which reflected left ventricular cavity potentials, there was elevation of the RS-T segment associated with depression of the RS-T segment in the standard limb and precordial leads. T waves in the leads at the atrial level, negative before exercise, became positive, behavior concomitant with inversion or flattening in the precordial leads. Esophageal leads reflecting the posterior surface of the left ventricle showed RS-T segment and T-wave changes similar to those seen in the precordial leads.

These results support the concept that the electrocardiographic changes after exercise result from changes localized mainly in the subendocardial aspect of the left ventricle.

CORTELL

Maroney, M., and Rantz, L. A.: The electrocardiogram in 679 healthy infants and children. Pediatrics **5:** 396 (March), 1950.

Electrocardiograms were taken on 679 apparently healthy children, ranging in age from six months to nine years. The P-R interval tended to increase in duration with advancing age. Nineteen children were found with P-R intervals of 0.16 or more. In these cases, no positive diagnosis of heart disease could be made. However, in this group 2 were classified as normal, 10 as having a slight or moderate suspicion of some active infection, possibly rheumatic fever, 5 as having definite suspicion of some active infection, possibly rheumatic fever, and 2 were considered probable cases of rheumatic fever. The authors state that it is rare for a P-R interval of 0.16 seconds or more to occur in a well child.

The QRS duration also tended to increase slightly with advancing age. In only 2 cases was the QRS duration less than .04 second (.03 second), and in only 2 was it greater than .08 second (.09 second).

In the standard limb leads, the axis deviation was greater than 90 degrees (98, 100 and 116 degrees) in 3 cases, and less than 0 degrees (-5, -10, and -30 degrees) in 3. In these 6 cases no evidence of heart disease was found.

The T and P waves were never flat, diphasic or inverted in Lead I. This was a common finding in Lead III. However, in Lead II the P waves were flat, inverted or diphasic in 6 cases in whom there was no evidence of heart disease.

MARGOLIES

HYPERTENSION

Ayman, D.: Critique of reports of surgical and dietary therapy in hypertension. J. A. M. A. **141:** 974 (Dec. 3), 1949.

The author calls attention to the lack of adequate control studies before and after treatment, in the case of the various reported results obtained with sympathectomy or dietary regimens in patients with hypertension. The most difficult point to establish is a dependable pretreatment basal level of blood pressure. Generally, the control period is too brief to be considered of value for this purpose.

It is the author's belief that, except in the occasional case, the low sodium diet and the rice diet are of little use. Sympathectomy has a definite effect on the blood pressure of some hypertensive persons.

ABRAMSON

Koepsell, J. E., Kuzma, J. F., and Murphy, F. D.: Hypertensive cardiovascular disease (acute) (malignant hypertension). Arch. Int. Med. **85:** 432 (March), 1950.

The authors present 39 cases of hypertensive cardiovascular disease (acute)—often called malignant hypertension—studied clinically and at autopsy. Special emphasis is placed on those cases showing

certain exceptions in the clinical course, such as a case of spontaneous remission, a case in which the classic changes of malignant hypertension were lacking from the eyegrounds and a case in which the cardiac changes developed before the onset of albuminuria and other evidences of renal disease.

The natural history and course of malignant hypertension are reviewed and show that some cases do not present the classical picture of the disease. The differentiation of chronic glomerulonephritis and brain tumor from malignant hypertension is discussed. The correct diagnosis of malignant hypertension can usually be made by a careful study of the history of the patient and the use of simple tests of renal function.

When an early diagnosis of malignant hypertension is made, radical sympathectomy is warranted. Early surgical treatment, especially in younger persons, is likely to be more satisfactory than that carried out late in the course of the disease or when the arteriosclerotic process is advanced.

BERNSTEIN

Chasis, H., Goldring, W., Breed, E. S., Schreiner, G. E., and Bolomey, A. A.: Salt and protein restriction. Effects on blood pressure and renal hemodynamics in hypertensive patients. J. A. M. A. **142:** 711 (March), 1950.

Twelve patients with essential hypertension, chosen at random, were maintained from 14 to 79 days on a diet of 2500 calories per day consisting approximately of carbohydrate, 250 to 300 Gm.; protein, 70 Gm.; fat, 85 Gm.; sodium chloride, 6 to 7 Gm.; until the blood pressure appeared to be stabilized. The patients were then placed on the rice diet described by Kempner for 14 to 98 days.

The rice diet appeared to produce an adverse effect on renal function. In 9 out of 10 subjects studied, the filtration rate decreased below the control level; the renal plasma flow decreased in 8 of 10 subjects, and increased slightly over the control level in 2. The maximal rate of tubular excretion of paraaminohippurate was reduced in 6 subjects. However, the effects on filtration rate and renal plasma flow appeared to be attributable to the low salt content of the diet, since the addition of sodium chloride (30 Gm. daily) to the rice diet of 5 subjects was followed by a return of the filtration rate toward the control level in all 5 patients, while the paraaminohippurate clearance returned to the control level in the 2 in whom this value had decreased significantly. However, the maximal rate of tubular excretion of paraaminohippurate showed a further decrease in 4 of the 5 patients when salt was added to the rice diet. It is possible that the low protein content of the rice diet or some specific dietary deficiency has an adverse effect on tubular function. When the original diet was reinstituted in 3 patients in whom the maximal rate of tubular excretion had been depressed, this function returned to, or near to, the control value.

The average systolic and diastolic blood pressure in the latter part of the rice diet period decreased, relative to the control pressure, in 4 of the 12 patients studied. However, in none of these could the decrease in pressure be attributed to the rice diet with certainty. A prompt and significant increase in systolic and diastolic pressure occurred in 4 of the 5 patients who were given sodium chloride daily while on the rice diet. This suggests that salt restriction may be more important than dietary restriction in effecting reductions in blood pressure.

KITCHELL

PATHOLOGY

Arrillaga, F. C., De Soldati, L., and Gandulla, L.: On four cases of myocarditis from Chagas' disease. Hev. argenta de cardiol. **17:** 29 (Jan.–Feb.), 1950.

Four patients, 2 men and 2 women between 47 and 59 years of age, with chronic myocarditis due to Chagas' disease (cardiac trypanosomiasis) are presented. In 3 of them, symptoms were practically absent; the fourth patient had symptoms caused by congestive heart failure which disappeared after the usual treatment. All of them had globular cardiac enlargement, no audible murmurs, and definite abnormalities of intraventricular conduction. Three cases had a tendency to hypotension. Ventricular extrasystoles were present in 3 cases, complete A-V block in 1, and auricular fibrillation in 1.

The etiologic diagnosis was arrived at on the following grounds: (a) absence of valvular lesions; (b) the fact that the patients had lived in districts infested by the vectors of trypanosomiasis; (c) electrocardiographic changes characteristic of cardiac trypanosomiasis; (d) positive complement fixation reaction with antigen of *S. cruzi*.

LUISADA

Sahn, S. H., and Levine, I.: Pulmonary nodules associated with mitral stenosis. Arch. Int. Med. **85:** 483 (March), 1950.

Two cases of pulmonary nodules associated with mitral stenosis are presented. The infrequency of this association is more apparent than real. Although the first patient exhibited the "soft" areas of infiltration and the second the "calcific" areas of density, according to the distinction maintained in the literature, the authors suggest that the conditions be interpreted as being due to the same basic changes. These consist of a combination of hemosiderosis, fibrosis, chronic congestive changes and engorged vessels, with the calcification and ossification representing a more extreme reaction to the degenerative changes.

The diagnosis is usually made during the asymptomatic period or when the patient is in mild failure.

The use of routine roentgenograms of the chest is recommended to determine the exact frequency of this complication. Patients with pulmonary areas of calcification should be given skin tests with histoplasmin and coccidioidin as well as with old tuberculin before a final diagnosis is made, but mitral stenosis must also be considered if it is present.

BERNSTEIN

Drake, E. H., and Lynch, J. P.: Bronchiectasis associated with anomaly of the right pulmonary vein and right diaphragm. J. Thoracic Surg. **19:** 433 (March), 1950.

The authors describe a case of bronchiectasis associated with a peculiar anomaly of the right diaphragm and right pulmonary vein. There was reduplication of the posterior portion of this diaphragm, an extra leaf arising from its dome and extending posterolaterally to join the chest wall 2 inches above the normal diaphragmatic reflection. The lower lobe of the right lung was therefore incompletely divided into 2 portions which were connected by an isthmus posteromedially. No true fissure was found between the upper and middle lobes, the middle lobe being replaced by two lingula-like processes which extended over the right cardiac border. In the fissure between the upper and anomalous lower lobes was a large inferior pulmonary vein which penetrated the diaphragm in front of the junction of the normal diaphragm and the anomalous septum to course along the inferior surface of the diaphragm and enter the inferior vena cava.

It was possible to resect the right lower lobe by the individual ligation technics leaving the anomolous inferior pulmonary vein intact.

KLOSK

PHARMACOLOGY

Friedman, A. P., Feising, E., Davidoff, L. M., Merritt, H. H.: Arteriographic study of effect of drugs on intracranial vessels in patients with chronic headache. A preliminary report. Arch. Neurol. & Psychiat. **62:** 818 (Dec.), 1949.

It is believed that certain types of headache are caused by aberrations in the caliber of the intracranial vessels. By means of arteriography the authors attempted to demonstrate roentgenographic variations caused by drugs in the size of the intracranial vessels of 8 patients. Diodrast itself caused no change in the caliber of the blood vessels. Histamine was shown to produce a pronounced dilatation of blood vessels in 2 of 4 patients. One of these patients developed a headache and flushing characteristic of histamine injection. Ergotamine tartrate was shown to produce a decrease in size of the blood vessels in 2 of 4 patients. The authors believe this may be a useful method for study of the various therapeutic agents in headache.

LECKS

Scébat, L., and Lenègre, J.: Action of morphine on right ventricular pressure in cardiac patients. Arch. d. mal. du coeur **42:** 1154 (Dec.), 1949.

A study of 30 cardiac cases was made by means of right heart catheterization. Morphine lowered both right auricular and right ventricular pressure in 26 cases; it increased these pressures in the other 8. No explanation was found for this result.

LUISADA

Tuchman, M. S., and Moolten, S. E.: Use of hyaluronidase in preventing the pain of subcutaneous heparin injection. Am. J. M. Sc. **219:** 147 (Feb.), 1950.

Heparin may be repeatedly administered subcutaneously without pain and with rapid effect on the coagulation time if the site of injection is first infiltrated with a small amount of hyaluronidase solution. The absorption rate and coagulation-time curves are almost identical with those produced by intermittent intravenous injections at the same intervals and in similar dosage. The procedure is relatively simple and easily carried out by the nursing staff. The authors found hyaluronidase infiltration effective in one case in aiding rapid resorption of a large painful hematoma.

DURANT

Kay, A. W., and Smith, A. N.: Effect of hexamethonium iodide on gastric secretion and motility. Brit. M. J. No. 4651: 460 (Feb.), 1950.

The authors studied the effects of hexamethonium iodide (C_6) and pentamethonium iodide (C_5), in doses of 30 to 40 mg. intravenously, on blood pressure, peripheral circulation, and sweating in 5 normal, 15 vasospastic and 7 hypertensive subjects. They also compared their effects with that of 250 to 500 mg. of tetraethylammonium bromide (TEAB) given intravenously to 6 normal subjects and 1 vasospastic subject. Responses to the former (C_5 and C_6) occurred in one to five minutes and continued for 30 to 120 minutes; these responses consisted of a fall in systolic and diastolic pressures. This reduction was considerably less than that produced by sodium amytal. Postural hypotension occurred one hour after injection and was more pronounced in the hypertensive group, but abated after two to four minutes of rest or walking. These investigators feel that this limits the therapeutic value.

With C_5 and C_6, the response varied in upper and lower extremities. In the former no significant increases in skin temperature and blood flow were noted, while in the latter a prolonged increase in blood flow and skin temperature occurred. The authors feel that these drugs are unlikely to be of value for investigation of upper limb vasospasm. On the lower limb, the effect of C_5 and C_6 was much greater and more constant than TEAB, and the antoward effects were less disturbing. Blood flow to

muscle was not greatly altered and sweating was lessened in the digits in which the temperature rose.

TANDOWSKY

Wilson, J. R., Harrison, C. R.: Cardiovascular, renal and general effects of large, rapid plasma infusions in convalescent men. J. Clin. Investigation **29:** 251 (Feb.), 1950.

The authors studied the adjustments of the cardiovascular and renal systems to large sudden increments in blood volume by giving infusions of 900 to 1955 cc. of reconstituted human plasma to 10 convalescent males during periods of time ranging from five and one-half to 60 minutes. These infusions were well tolerated. The sudden increase in blood volume was accompanied by a temporary elevation of the pulse rate, the respiratory rate, the blood pressure and the venous pressure. There was a fall in the hematocrit. Creatinine and paraaminohippurate clearances rose sharply following the infusions and then fell slowly, accompanied by a diuresis.

BUTTERWORTH

PHYSIOLOGY

Cullumbine, H.: Relationship between resting pulse rate, blood pressure and physical fitness. J. Applied Physiol. **2:** 278 (Nov.), 1949.

The author investigated the effects of exercise tests on the pulse rate and blood pressure of 1000 subjects. He found that the slower the resting pulse rate, the lower was the postexercise pulse rate. A similar relationship held between the resting and the postexercise systolic blood pressures. However, it was noted that the greater the resting systolic blood pressure, the greater was the speed of movement and the strength of performance of moderate exercise. The best performances were observed in sthenic subjects as compared with asthenic individuals.

ABRAMSON

Curtis, H. J.: Action potential of heart muscle. Am. J. Physiol. **159:** 499 (Dec. 1), 1949.

Small homogeneous bundles of muscle fibers from the turtle ventricle were isolated by microdissection technics. It was found that cardiac fibers do not behave as skeletal muscle fibers in that the heart muscle fiber remains depolarized for the period of contraction, and relaxation does not begin until repolarization is almost complete. This physiologic phenomenon of prolonged depolarization is true at the cellular level.

MOKOTOFF

Luisada, A. A., Mendoza, F., and Alimurung, M. M.: The duration of normal heart sounds. Brit. Heart J. 11: 41 (Jan.), 1949.

This report is based upon a study of 185 phonocardiograms of individuals with normal hearts. The authors suggest that, for practical purposes, the first sound and the second sound should be divided into three phases: the slow vibrations which form the beginning and the end of the complex, and the main or middle portion of the complex which consists of large irregular vibrations that are caused chiefly by valvular elements. The duration of large vibrations as well as the duration of the entire sound complex should be measured.

The average duration of the first sound was 0.146 second at the apex and 0.140 second at the aortic area. The average duration of the middle phase of the first sound was 0.060 second at the apex and 0.063 second at the aortic area. The average duration of the second sound was 0.097 second at the apex and 0.104 second at the aortic area. The average duration of the middle phase of the second sound was 0.023 second at the apex and 0.039 second at the aortic area. The average duration of the third sound was 0.059 second at the apex and 0.042 second at the aortic area.

SOLOFF

Kornerup, V.: Concentrations of cholesterol, total fat and phospholipid in serum of normal man. Arch. Int. Med. **85:** 398 (March), 1950.

The object of the investigation was to procure normal material for the determination of total cholesterol, free cholesterol, total fat and phospholipid in human serum. The series comprised 221 healthy, normal subjects, including 125 adults from 19 to 96 (87 men and 38 women) and 96 children from 1 to 16 years (51 boys and 45 girls). All sex-age groups were fairly equally represented except that of women from ages 40 to 60, which group was not represented at all. The anthropologic index calculated after Stromgen varied in the present material with increasing years up to the age of 50. The subjects measured were divided into three groups, one chiefly leptosomatic, one intermediary and one chiefly pyknic.

The absolute and relative amounts of phospholipid and phosphatides in serum were larger in children than in adults. There was a tendency toward higher serum lipid values in females than in males, in elderly than in young persons and in pyknic than in leptosomatic types. In children there was a tendency toward lower cholesterol concentration in serum. The differences, however, were small and, as a rule, not significant. The higher serum lipid values in elderly normal subjects than in young normal subjects may have been due to the presence of latent characreristic morbid alterations in pyknic subjects of the older age group.

BERNSTEIN

Roofe, P. G., Latimer, H. B., Madison, M., Maffet, M., and Wilkinson, P.: Comparison of peripheral blood with heart blood in guinea pigs. Science **111:** 337 (March 31), 1950.

The authors present further data on the differences existing in peripheral blood and heart blood as demonstrated in the study of 56 normal guinea pigs. They compared the number of red cells and white cells, and the percentage of lymphocytes and polymorphonuclear cells in blood taken from the ear and in blood from the heart. A significantly greater number of red and white cells was found in the peripheral blood as compared with the heart blood. Differential white cell counts showed no conclusive differences.

WAIFE

Kirk, E., and Praetorius, E.: Presence of phosphatase in the human aortic wall. Science **111:** 334 (March 31), 1950.

In the human aortic tissue definite phosphatase activity was best demonstrated enzymatically at a pH of 5.7 to 5.8. Previous estimations of phosphatase activity of arterial tissue have been made only under alkaline conditions.

WAIFE

Wilkinson, C. F., Jr., Blechs, E., and Reimer, A.: Is there a relation between diet and blood cholesterol? Arch. Int. Med. **85:** 389 (March), 1950.

The authors studied 83 persons from a family group in which essential familial hypercholesteremia was present. These subjects were given a diet of the individual's choice. The absolute amount of carbohydrate, fat, protein and cholesterol in the diet had no demonstrable relation to the level of total serum cholesterol. It was not possible to demonstrate that the percentage of total calories supplied by the various dietary constituents was related to the level of total serum cholesterol.

When hypercholesteremia is due to the heterozygous abnormality of essential familial hypercholesteremia, no adverse prognosis can be postulated. This is not true with the homozygous abnormality where atheromatosis may develop at an early age and be fatal. Hypercholesteremia per se has no demonstrable effect on life expectancy.

BERNSTEIN

RHEUMATIC FEVER

McEwen, C., Bunim, J., Baldwin, J. S., Kuttner, A. G., Appel, S. B., and Kaltman, A. J.: The effect of cortisone and ACTH on rheumatic fever. Bull. N. Y. Acad. Med. **26:** 212 (April), 1950.

Cortisone or ACTH was administered to 3 children with rheumatic fever and rheumatic heart disease. The fever, the erythrocyte sedimentation rate and the fibrinogen concentration in the blood fell. The serum globulin (increased in 2 patients before therapy) became normal during treatment. The "C" reactive protein and antistreptolysin O titer in 2 of the patients fell to normal as the patients improved.

The effect on rheumatic carditis was less definite. Two patients with active carditis of two and one-half and nine months' duration respectively, showed no immediate improvement in heart failure. The third patient, treated on the sixth day of rheumatic fever, showed striking improvement of carditis and apparently was completely well following 44 days of treatment.

WHITE

ROENTGENOLOGY

Grayson, C. E., and Kennedy, B. R.: Roentgen diagnosis of ruptured aneurysm of the abdominal aorta. Radiology **54:** 413 (March), 1950.

The authors describe the clinical and roentgenographic findings in 3 patients who died from rupture of arteriosclerotic abdominal aneurysms. Roentgenograms in 2 of the 3 cases showed calcification of parts of the aneurysmal wall; all 3 cases presented a marginated soft tissue density (hematoma) obliterating the usually well visualized shadow of the psoas muscle. Immediate survival after such rupture, permitting a surgical approach and corrective measures such as ligation or cellophane wrapping, apparently is not too unusual.

SCHWEDEL

Frimann-Dahl, J.: Roentgen examination in acute thrombosis. Radiology **54:** 408 (March) 1950.

The author describes a soft tissue roentgen technic applicable particularly in venous thrombosis of the extremities. Roentgenograms may be taken with the patient in bed, though better pictures may be obtained with the patient on a Bucky table. Usually 40 to 50 Kv. and 100 ma. are required with target film distance 90 to 100 cm. and time ½ second. Films of the opposite extremity are useful for comparison. The positive roentgenographic findings are: thickening of demonstrable subcutaneous fat, accentuation of reticulated subcutaneous structures, increased density of muscular shadows, obscuration of muscle margins, and broadening of the extremity. The changes are ascribed to edema and dilatation of subcutaneous vessels. The examination is easily performed and may be repeated to check the results of treatment.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Massell, T. B., Ettinger, J., and Voskamp, J. R.: A technique for extensive thoracolumbar sympathectomy without rib resection. Surgery **27:** 82 (Jan.), 1950.

The authors report a new operative technic for performing an extensive thoracolumbar sympathectomy without a rib resection. The ribs are separated gradually and the pleura is incised down to the diaphragm, which is also incised. The dissection is

carried caudad until the second lumbar sympathetic ganglion is mobilized. The dissection of the sympathetic chain is then carried cephalad until the mobilization of the upper thoracic sympathetic ganglia is completed.

According to the authors, an intercostal transpleural approach to the thoracolumbar sympathetic chain provides better exposure and causes less trauma than the commonly used retropleural approach with rib resection. Furthermore, there is a reduction in the incidence of complications with this procedure. The only contraindication to the operation is obliteration of the pleural cavity by a healed pleuritis.

ABRAMSON

Ferguson, L. K., and Holt, J. H.: Successful anastomosis of severed brachial artery. Am. J. Surg. **79**: 344 (Feb.), 1950.

The authors report a case of a gunshot injury to the brachial artery which was treated by an end-to-end anastomosis of the vessel. Shortly after the operation was terminated the hand became warm but the radial pulse did not return because the brachial artery was in severe spasm. After a stellate block was performed, this spasm disappeared and pulsations were obtained in the radial artery. During the postoperative period the patient received heparin and dicumarol, papaverine, and stellate blocks every 12 hours. When he left the hospital the brachial artery was still patent. However, it was necessary to perform repeated stellate blocks to counteract the vascular spasm which recurred for some time.

ABRAMSON

Carter, N., and MacMillan, B. G.: A technique for excision of the entire thickness of the ventricles of the heart—An experimental study. Surg. Gynec. & Obst. **90**: 282 (March), 1950.

A technic for excising portions of the entire thickness of the ventricular walls is presented with special emphasis on the incorporation of the pericardium in a loosely placed continuous mattress suture for closure of the defect. This technic was used in operating upon a series of 25 dogs. The operative mortality, in all cases due to ventricular fibrillation, was 12 per cent. There were no deaths due to technical failure. There was no instance of immediate technical failure with resulting hemorrhage.

The important measures in the prevention of ventricular fibrillation were found to be: (a) the liberal use of 2 per cent procaine solution on the surface of the heart and injected into the auricle, (b) the avoidance of displacement or angulation of the heart, and (c) the adequate oxygenation of the blood during the operative procedures on the heart.

After excision and suture, the wound in the heart healed first with a narrow band of scar tissue. Under the influence of the pressure within the ventricle, this band widened and thinned during the ensuing months. No instance of late rupture through this area or the development of aneurysm in this region has been discovered. Mural thrombi were not found in the chamber of the heart after suture.

The method has not been utilized on man, but the authors suggest that it could be applied clinically in cases of (a) small localized aneurysms such as might follow small infarcts or localized injury to the myocardium, (b) tumors of the heart, (c) encysted foreign bodies, and (d) acute injury to the myocardium producing an area of necrosis which would lead to subsequent rupture.

KLOSK

Temple, L. J.: Aneurysm of the first part of the left subclavian artery. J. Thoracic Surg. **19**: 412 (March), 1950.

The authors describe the successful ligation of the first part of a subclavian artery with aneurysmal involvement. This is the first reported operation by the direct transpleural approach to the first part of the subclavian artery. The usual exposure is made either anteriorly and above by dividing the sternomastoid after resecting a portion of the clavicle and splitting the manubrium 1 or 2 inches of the first rib, or by the posterior mediastinal approach with resection of the posterior end of the second and third rib and transverse process and stripping of the mediastinal pleura extrapleurally. The collateral circulation likely to take place after ligation of the first part of the left subclavian is described.

KLOSK

THROMBOEMBOLIC PHENOMENA

Soulié, P., Chiche, P., and Papanicolis, I.: Organized parietal thrombosis in the cavities of the heart. Arch. d. mal. du coeur **42**: 669 (July), 1949.

In 825 autopsies performed on patients with heart disease, the average incidence of mural thrombi was found to be 25 per cent. No definite clinical sign which would indicate formation of an intracardiac thrombus could be established. Fever, occurrence of emboli, cyanosis and cardiac arrhythmias were not reliable criteria for diagnosis.

In the rheumatic group, the incidence was greatest in pure mitral stenosis. No correlation could be established with the presence of auricular fibrillation or with activity of the rheumatic process. Cases with a slow evolution of the valvular lesion and with marked heart failure were more prone to the development of mural thrombi in the auricles. Intracardiac thrombi were relatively rare in subacute bacterial endocarditis; they were more common in hypertensive heart disease with coronary involvement associated with heart failure, and were extremely rare in congenital heart disease.

The authors are opposed to the systematic prophylactic use of anticoagulants in acute myocardial infarction. They feel that this treatment enhances

the detachment of friable particles of the thrombus and may thus lead to embolization.

PICK

Wilson, H.: Surgery for the prevention of pulmonary embolism. Am. J. Surg. **78:** 421 (Oct.), 1949.

According to the author, phlebothrombosis and thrombophlebitis are in reality extreme variations of the same process, with pulmonary embolism less likely to occur in the latter, because the associated inflammatory reaction present in the wall of the vein increases the probability of the clot becoming adherent to the wall. It is the author's belief that appropriate vein ligation in the patient with phlebothrombosis is the best method to prevent pulmonary embolism, while in the case of deep thrombophlebitis, unless the process is spreading very rapidly or an infected clot is present, conservative therapy should be carried out.

ABRAMSON

Snead, C. R., Lasner, J., Jenkinson, E. L., and de Takats, G.: Roentgen therapy of thrombophlebitis. J.A.M.A. **141:** 967 (Dec. 3), 1949.

One hundred patients with either superficial or deep thrombophlebitis of the lower extremities were treated with a short course of roentgen ray during the acute stage of the disease. The purpose of the therapy was to attempt to abort the acute lymphatic obstruction or lymphatic hyperplasia surrounding the thrombosed segment of vein. The procedure was used in conjunction with the conventional methods of treating thrombophlebitis. In 85 patients the therapy was considered to be successful since periphlebitic exudate subsided, pain was relieved and ambulation was possible. Generally one to six treatments were found necessary, with the optimal dose being 80 to 100 r.

According to the authors, the administration of a well timed and well planned dose of roentgen rays hastens the absorption of the inflammatory exudate and overcomes the blockade of lymph at isthmic points, such as the popliteal fossa and the groin. This type of therapy does not appear to affect the thrombus in the vein. However, since it causes the inflammation around the adventitia of the vessel to subside, it helps to remove the irritation of the vascular nerves found in this site, and hence it may produce relief of pain and reduction in reflex vasospasm.

ABRAMSON

Ochsner, A., De Bakey, M., De Camp, P. T., Richman, I. M., Ray, C. J., Llewellyn, R. C., and Creech, O.: Postphlebitic syndrome. Treatment by conservative measures, sympathectomy, and other operative measures. Surgery **27:** 161 (Feb.), 1950.

The authors studied 246 patients suffering from the postphlebitic syndrome. Edema was found in all, pain was noted in about two-thirds of the cases, while ulcers existed in one-third of the series. Persistent edema was found to be due either to vasospasm, to increased venous pressure because of incompetence of the valves of the deep veins, or to extensive perivenous cicatrix. The authors believe that if relief follows the use of vasodilating procedures, then vasospasm is probably the etiologic factor. If this does not occur, phlebographic studies are indicated to determine the presence or absence of incompetence of the valves of the deep veins and perivenous cicatrix.

In the present series 57 per cent of the patients were treated conservatively. The measures consisted of avoidance of vasoconstricting influences, such as smoking, exposure to cold, and emotional upsets. In addition, the patients were instructed to apply compression bandages before arising in the morning. In this group, 13.6 per cent became asymptomatic, 33.6 per cent were definitely improved, 44.3 per cent had slight or no change, and 8.5 per cent became worse in spite of therapy. In the remaining 43 per cent of cases sympathectomy was done, since vasospasm was apparently responsible for the persistence of symptoms. In this group, 20.8 per cent became asymptomatic and 35.8 per cent were definitely improved; 39.6 per cent had slight or no change and 3.8 per cent became worse. These findings were somewhat better than the findings in the patients who received conservative therapy.

ABRAMSON

VASCULAR DISEASE

Goetz, R. H.: The diagnosis and treatment of vascular diseases. With special consideration of clinical plethysmography and the surgical physiology of the autonomic nervous system. Brit. J. Surg. **37:** 146 (Oct.), 1949.

Normally the capacity of the cutaneous circulation is many times greater than that required to take care of the metabolic needs of the skin and subcutaneous tissue. Therefore, in order for trophic disturbances to develop, it is necessary for the cutaneous arteries to be practically occluded. In the case of the muscles, a moderate degree of interference with the arterial blood flow will produce intermittent claudication. For those individuals who develop threatening gangrene without ever having experienced intermittent claudication, the prognosis is grave, since it can be assumed that a marked degree of arterial obstruction exists.

The use of diathermy and other reflex vasodilatation methods is contraindicated in the presence of an extremity with a reduced circulation which has been sympathectomized, since, as a result of the removal of vasomotor tonus from the nonsympathectomized vessels, there will be a shunting of blood into these now more dilated arteries at the expense of the circulation to the sympathectomized limb. Contrary to the generally accepted opinion, the author believes that only in case of preganglionic

ramisections in the upper extremities do the vessels regain reflex vasomotor control, while in the cervicodorsal ganglionectomies they remain permanently sympathectomized. Furthermore, his results do not support the concept that hypersensitivity to adrenalin is responsible for the clinical relapse in patients with Raynaud's phenomenon who have been sympathectomized. With regard to therapy, sympathectomy is not indicated in those individuals in whom preliminary testing demonstrates complete occlusion of main vessels with a poor collateral circulation. In the presence of a good collateral circulation, sympathectomy should be carried out early and not as a last resort.

ABRAMSON

Robertson, R. L., Dennis, E. W., and Elkin, D. C.: Collateral circulation in the presence of experimental arteriovenous fistula. Surgery **27**: 1 (Jan.), 1950.

Blood flow was studied in the extremities of dogs by the plethysmographic method after arteriovenous fistulas were produced experimentally in the femoral vessels. With the fistula open the circulation to the distal portion of the extremity was found to be below normal. Temporary closure of the fistula produced a marked augmentation in flow.

The findings appeared to indicate that, following ligation of a fistula, a large collateral bed is generally immediately available for use and that, as a result of blood flow through it, adequate nutrition will be brought to the tissues distally. However, it is necessary to allow for the maximum development of collateral circulation before operation is performed on the arteriovenous fistula.

ABRAMSON

Lee, R. E., Holze, E. A.: The peripheral vascular system in the bulbar conjunctiva of young normotensive adults at rest. J. Clin. Investigation **29**: 146 (Feb.), 1950.

Because the authors felt that little direct information had been obtained regarding the reactivity and pattern of response to stimuli in the capillary blood vessels of man, they studied with a slit-lamp microscope and photographed at magnifications up to 62 × the bulbar conjunctiva on 51 normal young adults of both sexes between the ages of 21 and 34 years. They determined threshold concentrations of epinephrine which, when applied directly to the region, would just produce closure of the precapillary sphincters. Speed of blood flow and spontaneous vasomotor activity were also studied. Three photomicrographs are reproduced.

BUTTERWORTH

Anton, J. I., and Cooperman, H. H.: Carotid-jugular arteriovenous fistula. Am. J. Surg. **79**: 324 (Feb.), 1950.

An arteriovenous fistula between the common carotid artery and the internal jugular vein is a rare occurrence; only 65 cases have been reported in the literature. To this number the authors add another case which was successfully treated by quadruple ligature of artery and vein with complete excision of the fistula. The altered dynamics associated with this type of abnormal communication are discussed.

ABRAMSON

Leopold, S. S.: The etiology of pulmonary arteriolosclerosis (Ayerza's syndrome), with report of an illustrative case. Am. J. M. Sc. **219**: 152 (Feb.), 1950.

A case is reported in which the clinical features fulfilled all of the essential diagnostic criteria of Ayerza's disease. Pulmonary function studies were significant in that they tended to rule out significant pulmonary emphysema and indicated the presence of a pulmonary lesion, either alveolar or vascular, causing decrease in functioning lung tissue. At necropsy, there were changes in the aorta compatible with syphilis; there was marked hypertrophy of the right ventricle, and intimal proliferation of the small pulmonary arteries with reduction in their lumen, similar changes being absent from the small vessels of the greater circulation. In the author's opinion, this condition occurs most frequently in an individual with syphilitic infection, who has, in addition, a chronic infection of the lower respiratory tract. "Ayerza's syndrome" is the preferred designation for the disease because of the lack of precise knowledge of etiology.

DURANT

Wilens, S. L., and Elster, S. K.: The role of lipid deposition in renal arteriolar sclerosis. Am. J. M. Sc. **219**: 183 (Feb.), 1950.

In a study of 140 necropsies, it was found that lipid deposition occurs in the walls of renal arterioles as commonly as it does in the intima of large arteries. It is relatively infrequent and slight in the very young and increases in incidence slowly but progressively with advancing age in nonhypertensive subjects. The incidence is significantly increased in all forms of hypertension except that associated with chronic glomerulonephritis. It is significantly increased also in diabetes. It is not increased in renal disease that is not associated with hypertension. The incidence and severity is increased in the presence of arteriolar sclerosis, although scanty lipid deposits are frequently found in arterioles that are otherwise unaltered. Evidence is presented that indicates that lipid deposition may be an early and essential feature in the hyalinization and thickening of arterioles observed in protracted hypertension. It is further suggested that elevation of arteriolar blood pressure or increase of the plasma content of

lipid is an important factor in the deposition of fat within arteriolar walls.

DURANT

Schick, R. M., Baggenstoss, A. H., and Polley, H. F.: The effects of cortisone and ACTH on periarteritis nodosa and cranial arteritis: preliminary report. Proc. Staff Meet., Mayo Clin. **25:** 135 (March), 1950.

Cortisone was administered to 3 patients with periarteritis nodosa and to 2 with cranial arteritis; 2 others with periarteritis nodosa received ACTH. All 7 patients in whom the clinical diagnoses were confirmed by biopsy experienced prompt subjective relief after receiving the hormones; fever subsided within 24 to 72 hours and sedimentation rates decreased to normal more gradually. Partial relapses occurred in 5 patients after withdrawal of the hormones, followed by improvement when treatment was resumed. The other 2 are still receiving their initial course of hormonal therapy.

The 3 patients with periarteritis nodosa who received cortisone were critically ill when treatment was begun and, despite improvement, 2 died in cardiac and renal failure; the other has severe and progressive hypertension. The 2 patients who died were observed for 75 and 146 days and received 3.6 and 13.3 Gm. of cortisone, respectively. Necropsy showed complete healing of all arterial lesions, but, in the process of healing, fibrous obliteration of the lumens of these vessels had occurred, resulting in widespread visceral infarction. The adrenal glands of the patient who received the larger amount of cortisone were atrophied. Some evidence of hypercortisonism developed in most patients during treatment.

SIMON

Keil, P. G., Voelker, C. A., and Schissel, D. J.: Diagnostic value of pulmonary arteriography in bronchial carcinoma. Am. J. M. Sc. **219:** 301 (March), 1950.

In 14 of 15 cases of bronchial carcinoma, diminished vascularity of the portion of involved lung distal to the tumor mass was found on pulmonary arteriographic examination. Less frequently there was found decreased caliber of vessels with displacement, distortion and obstruction of the main pulmonary artery. Diminished vascularity was also found to occur in non-neoplastic diseases, notably senile pulmonary emphysema, bullous emphysema, and lung abscess. However, there was no difficulty in distinguishing the pattern of these conditions from that of carcinoma. It is believed that this method of study should be added to the diagnostic armamentarium in cases of suspected bronchial carcinoma.

DURANT

Berthong, M., Rich, A. R., and Griffith, P. C.: A study of the effect of adrenocorticotropic hormone upon the experimental cardiovascular lesions produced by anaphylactic hypersensitivity. Bull. Johns Hopkins Hosp. **86:** 131 (March), 1950.

Because anaphylactic hypersensitivity may be an important factor in the pathogenesis of the collagen-vascular diseases, and because the adrenal cortical hormone has been shown to have dramatic therapeutic effect on certain diseases of this group, it was decided to determine whether this hormone would affect the development of the lesions of periarteritis nodosa which can be produced by anaphylactic hypersensitivity.

Forty albino rabbits were sensitized by a single intravenous injection of 10 cc. of sterile horse serum per kilogram of body weight. One half of these rabbits were treated for 15 to 18 days with intramuscular injections of adrenocorticotropic hormone. The other 20 rabbits were used as normal controls. In 90 per cent of the untreated control animals, marked vascular or cardiac lesions, or both, were found. However, in the animals treated with adrenocorticotropic hormone, only 25 per cent of the animals revealed lesions. As a result of the activity of the hormone, the average weight of the adrenal glands in the treated group was 47 per cent greater, and the average weight of the thymus was markedly less, than that in the control group.

The authors conclude that while these results indicate that adrenocorticotropic hormone exerts an inhibitory effect upon the development of the cardiovascular lesions of hypersensitivity, further studies are required before this conclusion can be verified.

MARGOLIES

MISCELLANEOUS

Callebaut, C., Denolin, H. and Lequime, J.: Application of the oxymetric method in the study of cardiopulmonary diseases, Arch. d. mal. du coeur **42:** 723 (July), 1949.

The oxymetric method permits the continuous determination of variations in the oxygenation of the blood in the periphery. The authors found that congenital heart disease with a venoarterial shunt a marked desaturation occurs following exercise, the degree of change being dependent on the size of the shunt. In some cyanotic cases, an increase in saturation was noted in the squatting position. This increase was not found following a successful operation. If used together with unilateral bronchospirometry, the oxymetric method permits precise conclusions on the functional capacity of the lungs.

Objective values for the arm-to-ear circulation time can be obtained by oxymetry following intravenous injection of methylene blue (normal value 10 to 15 sec.). The circulation time from the lungs to the ear can be determined from the sudden drop

of peripheral oxygen saturation following inhalation of an oxygen-poor gas mixture or following a short period of voluntary apnea. The circulation time from lungs to ear was found to be on the average 5.2 sec. in normal subjects.

PICK

Gordon-Taylor, G.: The war collection. Brit. J. Surg. **37:** 129 (Oct.), 1949.

The author describes the collection of specimens, photographs and pen and ink illustrations of World War II wounds found in the Royal College of Surgeons' Museum in England. Included are the hearts of victims of Belsen concentration camp showing marked reduction in size of the walls of the chambers and of the great vessels, and brown atrophy of the muscle. A number of heart specimens demonstrate the effect of penetration of metal projectiles and rupture following injury to the chest. Examples of various types of involvement of the main vessels in the body are also present, including arterial and arteriovenous aneurysms and traumatic dissecting aneurysms. Abdominal injuries associated with perforation and destruction of intestines and penetration of the liver and gall bladder by bullets are illustrated in color photographs. Numerous specimens of trauma to the brain, as well as the reaction of the skin and eyes to mustard gas, are also presented.

ABRAMSON

Borst, J. R.: Disturbances in water and salt metabolism in the final stage of chronic renal insufficiency. Acta med. Scandinav. **136:** 1 (Nov.), 1949.

The author presents the record of a 42 year old man suffering from chronic renal insufficiency and uremia, caused by bilateral cystic disease of the kidneys, in whom significant changes in the metabolism of water and salt were present. In an effort to combat severe dehydration, large amounts of water and sodium chloride were administered; the urinary output rose to 10 liters and 75 Gm. of sodium chloride daily in spite of a low plasma sodium level and a urea clearance of 8 to 10 per cent of normal. The use of a protein poor, high caloric diet, 10 to 20 Gm. of sodium chloride, 3 to 10 Gm. of sodium bicarbonate and as much as 8 to 11 liters of glucose in saline intravenously daily, resulted in a fall in the blood urea level from 600 to 40 mg. per cent and the prevention of dehydration, without the formation of edema or rise in blood pressure. Injection of desoxycorticosterone had no effect on the sodium chloride excretion. The patient died of miliary tuberculosis 7 months after his admission to the hospital. At autopsy the residual renal tissue revealed glomeruli which appeared to be practically intact whereas the tubules, especially the proximal convoluted tubules, showed severe degenerative changes. The suprarenal glands were normal in structure and contained only a few epithelioid-cell tubercles. A suprarenal cortex insufficiency could, with a fair degree of certainty, be excluded as the cause of the disturbance in the water and salt metabolism. On the basis of the kidney findings it was postulated that although the glomerular activity was greatly impaired, the changes in the function of the tubules would dominate the clinical picture. This hypothesis was supported to a certain extent by the clinical picture, where the disturbed reabsorption of water and salts by the tubules predominated, though glomerular filtration was already severely reduced.

SCHWARTZ

Chapman, W. P., Livingston, R. B., Livingston, K. E.: Frontal lobotomy and electrical stimulation of orbital surface of the frontal lobes. Effect on respiration and on blood pressure in man. Arch. Neurol. & Psychiat. **62:** 701 (Dec.), 1949.

The authors studied the relation of the cortical areas in the frontal lobes to autonomic regulation in patients who were lobotomized for psychiatric disease. This study was concerned first with the effect of frontal lobotomy on the blood pressure and subsequently with the response of the blood pressure and respiration to electrical stimulation of the orbital surface of the frontal lobes. The results showed no consistent change in blood pressure levels after frontal lobotomy. Electrical stimulation of the orbital surface of the frontal lobes produced an elevation of the blood pressure in 6 to 9 patients and a cessation or diminution of respirations in expiration in 7 of 9 patients. These effects occurred simultaneously in 2 patients. In 4 patients the blood pressure elevation occurred independently of the respiratory effect. In 5 of 7 patients the changes were independent of a change in blood pressure during a given stimulus. The elevation of the blood pressure was not marked but it was still 3.6 times as great as the maximal spontaneous variation for systolic blood pressure and 3.4 times as great as the maximal spontaneous variation for the diastolic blood pressure.

LECKS

Hellerstein, H. K., and Liebow, I. M.: Electrical alternation in experimental coronary artery occlusion. Am. J. Physiol. **160:** 366 (Feb.), 1950.

Within two minutes after experimental occlusion of a coronary artery, electrical alternation developed in 8 of 9 dogs. Alternation usually involved the RS-T segment only and was occasionally precipitated by extrasystoles. The experiments confirmed Lewis' earlier postulates of partial refractoriness of injured cardiac tissue, sections of which may fail to respond to every second stimulus. Repeated temporary occlusions predisposed the animals to the development of alternation. In some instances injury effects were present at alternate beats only, which suggests that the injured region as a whole failed to respond to alternate excitation. The study

is based on direct electrograms of the epicardial and endocardial regions.

HECHT

Davidson, C. S., Gibbons, T. B., and Faloon, W. W.: Systemic and portal venous pressures in cirrhosis of the liver. J. Lab. & Clin. Med. **35**: 1811 (Feb.), 1950.

The blood pressure was measured in the antecubital, femoral, and superior abdominal collateral veins of 10 patients with chronic alcoholic cirrhosis of the liver and of one patient with a large ovarian cyst. If ascites was present, the ascitic fluid pressure was measured.

The antecubital venous pressure was within normal limits in 7 patients and slightly elevated in 4 patients. The femoral venous pressure was as high as, or higher than, the abdominal fluid pressure. The presence and extent of the edema of the lower extremities roughly correlated with the femoral vein and abdominal fluid pressure in 9 of the 11 patients. The abdominal collateral vein pressure, measured when free flow of blood through the vein was allowed, was usually below the ascitic fluid pressure. In all patients with cirrhosis, the pressure in the abdominal collateral vein when measured with proximal manual obstruction to the blood flow was as high as, or higher than, the ascitic fluid pressure. It remained elevated after paracentesis and was in the same range as the portal vein pressures obtained directly at operation. The pressure was elevated in the patient with the ovarian cyst, but fell promptly when the cyst was drained. The obstructed collateral vein pressure was generally highest in patients with the shortest interval between paracenteses. The serum albumin concentration did not correlate with the ascitic fluid pressure nor with the rate of ascites formation.

The authors conclude that the increased femoral and portal vein pressures are a factor in, but cannot alone account for, the formation and maintenance of edema or ascites.

MINTZ

AMERICAN HEART ASSOCIATION, INC.

1775 BROADWAY, NEW YORK 19, N. Y.

Telephone Plaza 7-2045

A.H.A GRANTS-IN-AID

Applications for American Heart Association Research Grants-in-Aid, including grants to basic sciences not directly related to the cardiovascular field, may be filed up to December 15, 1950. Information and forms may be obtained from the Medical Director.

EXECUTIVE COMMITTEE

The following have been elected to the Executive Committee of the Association's Board of Directors: A. W. Robertson, Pittsburgh, Chairman of the Board; Dr. Howard B. Sprague, Brookline, Mass., President of the Association; Dr. Louis N. Katz, Chicago, President-Elect; Dr. Maurice Visscher, Minneapolis, Vice-President; Dr. John J. Sampson, San Francisco, Secretary; Grant Keehn, New York, Treasurer; Dr. H. M. Marvin, New Haven, Chairman of the Scientific Council; Dr. Hugh McCulloch, Chicago; Dr. Robert W. Wilkins, Boston; Alva Bradley, Cleveland; Douglas B. Marshall, Houston; Robert L. Mehornay, Sr., Kansas City; Don G. Mitchell, Summit, N. J.; Frederick K. Trask, Jr., New York; Sylvester L. Weaver, Jr., New York; and Dr. Irving S. Wright, New York.

SCIENTIFIC COUNCIL

The Scientific Council of the Association has re-elected Dr. Howard B. Sprague, Brookline, Mass., and Dr. Harland G. Wood, Cleveland, for a five-year term on its Research Committee.

Re-elected to the Executive Committee of the Scientific Council were Dr. Daniel C. Elkin, Atlanta, Dr. Norman E. Freeman, San Francisco, and Dr. Morton F. Mason, Dallas.

A new pamphlet containing the Rules and Regulations of the Scientific Council has been issued and is available on request to the Association.

COMMITTEE ON ANTICOAGULANTS

A grant of $25,000 a year to the Committee on Anticoagulants for the next two years has been approved by the Association's Board of Directors. Dr. Irving S. Wright, New York Hospital, is Chairman of the Committee which is conducting a cooperative study of the new anticoagulants. Other members of the Committee include Nelson Barker, M.D., Mayo Clinic, Rochester, Minn.; F. Janney Smith, M.D., Henry Ford Hospital, Detroit; Hugh Luckey, M.D., Bellevue Hospital, New York; Harold Feil, M.D., Lakeside Hospital, Cleveland; E. Sterling Nichol, M.D., Jackson Memorial Hospital, Miami; Joseph Vander Veer, M.D., Pennsylvania Hospital, Philadelphia; Grafton Burke, M.D., New York Hospital, New York; Dorothy Beck, Ph.D., Statistician; Ralph Overman, Ph.D., Chemist, Consultant.

PENICILLIN PROPHYLAXIS FOR BACTERIAL ENDOCARDITIS

A statement approved by the American Council on Rheumatic Fever of the American Heart Association recommends specific dosage for the administration of penicillin before dental extractions and removal of tonsils and adenoids in patients with rheumatic heart disease or congenital heart or blood vessel defects to prevent the possible development of subacute bacterial endocarditis. The text of the statement follows:

Following dental extractions and removal of tonsils and adenoids, bacteria are frequently present in the blood stream for short periods of time. In rheumatic individuals or in patients with congenital heart disease these bacteria may lodge in the heart valves and cause bacterial endocarditis. Although a variety of bacteria cause this disease, the majority of cases are due to alpha streptococci (streptococcus viridans). Alpha streptococci are usually resistant to sulfa drugs. Penicillin is, therefore, recommended for prophylaxis. (1) Except in emergencies operative procedures in rheumatic individuals should be deferred until there is no clinical evidence of rheumatic activity and laboratory tests indicate that the rheumatic process is subsiding. (2) Patients should be free from upper respiratory infection. (3) Minimum dosage of penicillin: (a) 300,000 units of aqueous penicillin intramuscularly 30–60 minutes before extraction or operation. (b) 300,000 units of procaine penicillin in oil injected intramuscularly at the same time in a different site.

Penicillin prophylaxis is not necessary for the extraction of deciduous incisors or bicuspids unless infection of the gum is present. It should be used for the extractions of deciduous molars, all permanent teeth and for tonsillectomy and adenoidectomy. In most instances it is best to extract one tooth at a time; multiple extractions should be avoided. In cases of extensive gum infection or severe root infections (apical abscesses) it is advisable to give several doses of penicillin starting the day before operation and continuing one or two days thereafter.

Women with rheumatic or congenital heart disease should received penicillin prophylaxis at the time of delivery. It is also recommended for patients requiring gastrointestinal surgery.

NEW HEART ASSOCIATIONS

The Board of Directors of the Association has approved the affiliation of the Akron District Heart Association, California Heart Association, and Kentucky Heart Association.

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

PROGRAM OF THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

TO BE HELD IN

CHICAGO, ILL., NOVEMBER 5–6, 1950

NOVEMBER 5, 1950

MORNING

(E. Cowles Andrus, Presiding)

8:30–9:30
Registration

9:30–9:40
Opening Session

9:40–9:55
FACTORS INFLUENCING THE ATHEROSCLEROTIC PROCESS. J. B. Firstbrook, Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada.

9:55–10:00
Discussion

10:00–10:15
A STUDY OF LECITHIN AND ALBUMIN AS STABILIZERS OF CHOLESTEROL SOLS AND OF THEIR USEFULNESS IN THE PROPHYLAXIS OF EXPERIMENTAL ATHEROSCLEROSIS. O. J. Pollak, Department of Experimental Pathology Quincy City Hospital, Quincy, Mass.

10:15–10:20
Discussion

10:20–10:35
THE ACCUMULATION OF COLLOIDAL THORIUM DIOXIDE IN THE LESIONS OF EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS. G. Lyman Duff and Gardner C. McMillan, Department of Pathology, Pathological Institute, McGill University, Montreal, Canada.

10:35–10:40
Discussion

10:40–10:55
THE LIPID COMPOSITION OF TISSUE LYMPH IN NORMAL AND IN HYPERLIPEMIC RABBITS. Aaron Kellner and D. C. Dju Chang, Department of Pathology, The New York Hospital, Cornell Medical Center, New York, N. Y.

10:55–11:00
Discussion

11:00–12:00
LIPOPROTEINS AND ATHEROSCLEROSIS. John W. Gofman, Division of Medical Physics, Donner Laboratory, University of California, Berkeley, Calif.

12:00–12:15
Discussion

AFTERNOON

(Irvine H. Page, Presiding)

2:00–2:30
Business Session

2:30–2:45
ULTRACENTRIFUGE AND ELECTROPHORETIC STUDIES OF SERUM LIPOPROTEINS IN RELATIONSHIP TO VASCULAR DISEASE. Lena A. Lewis and Irvine H. Page, Research Division of the Cleveland Clinic Foundation and Frank E. Bunts Educational Institute, Cleveland, Ohio.

2:45–2:50
Discussion

2:50–3:05
THE COMPARATIVE METABOLISM OF DIETARY AND ENDOGENOUS CHOLESTEROL DIFFERENTIATED BY USE OF RADIOACTIVE CARBON. R. Gordon Gould, Rush Department of Biochemistry, The Presbyterian Hospital, Chicago, Ill.

3:05–3:10
Discussion

3:10–3:25
EFFECT OF DIETARY CHOLESTEROL ON RATE OF CHOLESTEROL SYNTHESIS IN THE INTACT ANIMAL MEASURED BY MEANS OF RADIOACTIVE CARBON. C. Bruce Taylor and R. Gordon Gould, Rush Department of Biochemistry, The Presbyterian Hospital, Chicago, Ill.

3:25–3:30
Discussion

3:30–3:45
THE EFFECT OF SALT-INDUCED HYPERTENSION ON SPONTANEOUS ATHEROSCLEROSIS IN THE CHICK. Jeremiah Stamler and Louis N. Katz with the technical assistance of Philip Johnson, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

3:45–3:50
Discussion

3:50–4:05
VASCULAR LESIONS IN ALLOXAN DIABETIC RATS. A. L. Chute, J. L. Orr, M. J. O'Brien and E. E. Jones, Hospital for Sick Children, Toronto, Canada.

4:05–4:10
Discussion

4:10–4:25
VASCULAR HYPERSENSITIVITY TO ADRENALIN AFTER RENAL INFARCTION IN RATS. Dorothy Loomis, Department of Pathology, State University of New York, New York College of Medicine, Brooklyn, N. Y.

4:25–4:30
Discussion

4:30–4:45
EXPERIMENTAL ARTERIAL LESIONS IN DOGS RELATED TO DIET AND RENAL INSUFFICIENCY. Russell L. Holman, Department of Pathology, Louisiana State University School of Medicine, New Orleans, La.

4:45–4:50
Discussion

4:50–5:05
THE GRANULAR CELLS OF THE RENAL ARTERIOLE AND HYPERTENSION. J. F. A. McManus, Department of Pathology, University of Virginia School of Medicine, Charlottesville, Va.

5:05–5:10
Discussion

7:30–10:30
Annual Dinner

NOVEMBER 6, 1950

MORNING

(G. Lyman Duff, Presiding)

9:30–9:40
Opening Session

9:40–9:55
WHITE BLOOD CELLS IN OLD AGE AND IN ARTERIOSCLEROSIS. Rudolf Altschul, Department of Anatomy, University of Saskatchewan, Saskatoon, Canada.

9:55–10:00
Discussion

10:00–10:15
MEDIAL DEGENERATION OF THE CORONARY ARTERIES OF CHICKENS: LESION OR ARTEFACT? J. C. Paterson, Department of Medical Research of the University of Western Ontario, London, Canada.

10:15–10:20
Discussion

10:20–10:35
PRODUCTION OF EXPERIMENTAL CHOLESTEROL-INDUCED ATHEROSCLEROSIS IN THE CHICK WITH MINIMAL HYPERCHOLESTEROL-

EMIA AND ORGAN LIPIDOSIS. Jeremiah Stamler and Louis N. Katz with the technical assistance of Christine Bolene, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

10:35–10:40
Discussion

10:40–10:55
THE EFFECT OF TWEEN 80 ON THE SERUM LIPIDS AND THE TISSUES OF CHOLESTEROL-FED RABBITS. Torrence P. B. Payne and G. Lyman Duff, Department of Pathology, Pathological Institute, McGill University, Montreal, Canada.

10:55–11:00
Discussion

11:00–11:15
THE EFFECT OF CHOLINE AND INOSITOL UPON EXPERIMENTAL CANINE ARTERIOSCLEROSIS. Jack D. Davidson, Walter Meyer and Forrest E. Kendall, Columbia Research Service, Goldwater Memorial Hospital, New York, N. Y.

11:15–11:20
Discussion

11:20–11:35
THE RELATIONSHIP BETWEEN THE PHOSPHOLIPIDS AND THE CHOLESTEROLS IN HUMAN PLASMA. Raymond S. Jackson, Charles F. Wilkinson, Jr., Eugene A. Hand, A. M. Waldron and William C. Vogel, Department of Medicine, New York University Post-Graduate Medical School, New York, N. Y.

11:35–11:40
Discussion

11:40–11:55
THE PHOSPHOLIPID-CHOLESTEROL RATIO AS A TEST FOR ATHEROSCLEROSIS. Lester M. Morrison, P. Gonzalez and E. Wolfson, Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists, Los Angeles, Calif.

11:55–12:00
Discussion

AFTERNOON

(Louis N. Katz, Presiding)

2:00–2:15
ATHEROSCLEROSIS OF EARLY AGE: CLINICAL AND PATHOLOGICAL STUDIES. David Adlersberg and F. G. Zak, The Medical Services and The Laboratories, Division of Pathology, of the Mount Sinai Hospital, New York, N. Y.

2:15–2:20
Discussion

2:20–2:35
THE AGE FACTOR IN CHOLESTEROLEMIA AND ATHEROMATOSIS IN THE CHICK. Simon Rodbard, Christine Bolene, Ruth Pick, Martin Lowenthal, Gerard Gros and Louis N. Katz, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

2:35–2:40
Discussion

2:40–2:55
FACTORS IN THE DEVELOPMENT OF PREMATURE VASCULAR DISEASE IN YOUNG DIABETICS. Howard F. Root and James Wilson, Boston, Mass.

2:55–3:00
Discussion

3:00–3:15
SERUM LIPIDS AND ATHEROSCLEROSIS IN DIABETES MELLITUS. Julius Pomeranze and Henry G. Kunkel, New York Medical College and the Hospital of the Rockefeller Institute for Medical Research, New York, N. Y.

3:15–3:20
Discussion

3:20–3:35
INCIDENCE OF HEREDITARY HYPERCHOLESTEROLEMIA. David Adlersberg, Louis E. Schaefer, Stanley R. Drachman and Rhoda Dritch, The Mount Sinai Hospital, New York, N. Y.

3:35–3:40
Discussion

3:40-3:55
THE EFFECTS OF LOW FAT–LOW CHOLESTEROL DIETS ON THE SERUM LIPIDS. Lester M. Morrison, M. Zwierlein and E. Wolfson, Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists, Los Angeles, Calif.

3:55–4:00
Discussion

4:00–4:15
STUDIES IN CLINICAL ATHEROMATOSIS. IV. IMPORTANT ROENTGENOLOGIC SIGNS. Joseph B. Wolffe, Wolffe Clinic and Hospital, Philadelphia, Pa.

4:15–4:20
Discussion

4:20–4:35
A COMPARISON OF AGING PROCESSES IN THE PULMONARY ARTERY AND AORTA. H. T. Blumenthal, Fred P. Handler, Jack Zuckner and S. H. Gray, Department of Pathology, St. Louis University, School of Medicine, The Laboratory of the Jewish Hospital, and the Snodgras Laboratory, City Hospital, St. Louis, Mo.

4:35–4:40
Discussion

4:40–5:00
Closing Session.

TO BE READ BY TITLE

SPONTANEOUS CANINE ARTERIOSCLEROSIS. Margaret Bevans, Bruce Taylor* and Liese L. Abell, Columbia Research Service, Goldwater Memorial Hospital, New York, N. Y. (*and Department of Pathology, Rush Memorial School, Chicago, Ill.)

PLASMA IODINE FRACTIONS AND PLASMA AND HEPATIC CHOLESTEROL IN RABBITS. Helen Bennett Brown and Irvine H. Page, Research Division and Frank E. Bunts Educational Institute, Cleveland Clinic Foundation, Cleveland, O.

FURTHER STUDIES ON THE HUMAN AORTIC PHOSPHATASE. John Esben Kirk and Elith Praetorius, Division of Gerontology, Washington University School of Medicine, St. Louis, Mo.

A CLINICAL COMPARISON OF 3 TESTS FOR ATHEROSCLEROSIS. Lester M. Morrison, Harry Sobel and E. Wolfson, Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists.

THE EFFECT OF LIPOTROPIC AGENTS (CHOLINE, INOSITOL) AND ESTROGENIC HORMONES IN SERUM LIPID FRACTIONS. Lester M. Morrison and E. Wolfson, Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists.

THE RELATIONSHIP OF CHOLESTEROL ESTERASE TO ATHEROSCLEROSIS. Lester M. Morrison, E. Wolfson and P. Berlin, Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists, Los Angeles, Calif.

THE EFFECTS OF CHOLESTEROL FEEDING DURING PREGNANCY ON BLOOD CHOLESTEROL LEVELS AND PLACENTAL VASCULAR LESIONS. Campbell Moses, Addison H. Gibson Laboratory, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.

THE EFFECT OF INGESTED ALUMINUM HYDROXIDE ON CHOLESTEREMIA AND ATHEROMATOSIS IN THE CHICK. Simon Rodbard, Christine Bolene, Ruth Pick and Louis N. Katz, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

THE ACTION OF SAPONIN UPON SERUM FROM ATHEROSCLEROTIC AND NONATHEROSCLEROTIC INDIVIDUALS. Harry Sobel and Lester M. Morrison, Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists.

THE EFFECT OF DESOXYCORTICOSTERONE ON CHOLESTEROL METABOLISM AND ATHEROSCLEROSIS IN THE CHICK. Jeremiah Stamler and Louis N. Katz, with the technical assistance of Eva Levinson, Marilyn Dudley and Grady Crowley, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

PROCEEDINGS OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

ABSTRACTS

Factors Influencing the Atherosclerotic Process

J. B. Firstbrook, Toronto, Canada

Banting and Best Department of Medical Research, University of Toronto

Factors influencing the development of aortic atherosclerosis have been investigated in rabbits fed cholesterol in uniform daily dosage. An increased extent of lesions was associated with high average blood total cholesterol level, high initial body weight, and rapid rate of weight-gain. In rabbits with similar initial body weights, similar rates of weight-gain, and receiving cholesterol for the same length of time, the extent of lesions was directly proportional to the average blood total cholesterol level. However, when initial body weights and rates of weight-gain varied from animal to animal, the correlation between blood cholesterol level and extent of lesions was relatively poor. It is suggested that the failure of many workers to find a positive correlation between blood cholesterol levels and severity of atherosclerosis in humans is due not only to variations in age among subjects but also to variations in adiposity among different subjects and in the same subject from time to time.

A Study of Lecithin and Albumin as Stabilizers of Cholesterol Sols and of Their Usefulness in the Prophylaxis of Experimental Atherosclerosis

O. J. Pollak, Quincy, Mass.

Department of Experimental Pathology, Quincy City Hospital

Biochemical and anatomic studies of rabbits injected intravascularly with serum containing cholesterol, sodium stearate or graphite in colloidal particles of varying size lent support to the concept that atherosclerosis can be initiated in rabbits by plasmatic dyscolloidity.

Whether such dyscolloidity is due to the presence of macromicels of cholesterol, cholesterol esters, cholesterol-alpha$_1$-globulin or cholesterol-beta$_1$-globulin, of chylomicrons of vegetable or animal nature, or of nonlipid substances, prophylactic attempts can be based on stabilization of colloids.

Lecithin, albumin, and bile salts are three naturally occurring substances which deserve priority in prophylactic attempts. Lecithin used in physiologic doses has no stabilizing effects in vitro or in vivo. Intravascular injection of lecithin—alone or together with cholesterol—results in vascular alterations which are strikingly different from those induced by cholesterol.

Albumin is an excellent in vitro stabilizer of cholesterol sols. Serum albumin injected intravascularly into rabbits in physiologic proportion to cholesterol proves a useful stabilizer of cholesterol in our experiments. The prophylactic action of albumin depends upon the amount of other protein fractions present in the medium.

The Accumulation of Colloidal Thorium Dioxide in the Lesions of Experimental Cholesterol Atherosclerosis

G. Lyman Duff and Gardner C. McMillan, Montreal, Canada

Department of Pathology, Pathological Institute, McGill University

A study was made of the distribution of intravenously injected colloidal thorium dioxide (Thorotrast) in rabbits with experimental cholesterol atherosclerosis of the aorta. The animals received a single intravenous injection of Thorotrast in an amount of about 3 cc. per Kg. of body weight five minutes to four days before death. Several normal rabbits were similarly injected for control purposes.

It was found that Thorotrast was not present in the aortic intima of the control animals nor in the normal areas of aortic intima between atherosclerotic plaques in the animals fed cholesterol. It was present in the foam-cells of the arterial lesions and in some of the endothelial cells covering these lesions. Its earliest appearance was at 20 minutes after injection and it became more clearly visible and more concentrated with longer lapses of time. It occurred only in the superficial layers of cells.

These preliminary observations confirmed the widely held belief that the foam-cells in atherosclerotic lesions are capable of accumulating particulate matter and established that they did so with surprising rapidity. Those cells closest to the lumen of the aorta accumulated the Thorotrast first and in the greatest amounts indicating that it had diffused from the lumen. The occurrence of Thorotrast only in those endothelial cells overlying plaques of foam-cells indicated that these cells were different from their neighbors with respect to the accumulation of particulate matter. Whether this difference was inherent or acquired has not been definitely determined. The rapidity of the deposition of Thorotrast as well as the high specific gravity of thorium dioxide speaks against the pathogenetic concepts of Leary and of Gordon.

The Lipid Composition of Tissue Lymph in Normal and in Hyperlipemic Rabbits

Aaron Kellner and D. C. Dju Chang, New York, N. Y.

Department of Pathology, New York Hospital, Cornell Medical Center

The lipids that precipitate within the intima of blood vessels during the development of atherosclerosis are lipids that have crossed an endothelial membrane and passed out of the blood stream into the tissue spaces of the artery wall. There have been very few studies of the lipid content of the extracellular fluid in the normal animal or during hyperlipemia, and of the permeability of the endothelium to lipid particles. A technic has been devised for cannulating the lymphatics of the lower leg of rabbits whereby it has been possible to obtain sufficient tissue lymph for detailed lipid analyses.

Tissue lymph and blood serum were obtained from normal rabbits and from rabbits with hyperlipemia following prolonged cholesterol feeding or the intravenous injection of detergents, and the content of cholesterol, cholesterol esters, lipid phosphorus and total lipid carbon in each was determined. In normal rabbits it was found that the lipid of the tissue lymph was about one-third that of the blood serum, and that this proportion was the same for each of the major lipid components. In the hyperlipemic rabbits, though the absolute amount of lipid in the tissue lymph was increased, the relative amount as compared to that of the blood serum was decreased and ranged from 5–20 per cent of the serum lipid. Also, in the hyperlipemic rabbits the relative distribution of cholesterol, phospholipid, and neutral fat between serum and lymph varied widely. In general, it appeared that the endothelium was more permeable to phospholipids than to cholesterol or neutral fat. In every case where the blood

serum was milky, the tissue lymph obtained at the same time was perfectly clear, indicating that large lipid particles (chylomicrons) did not readily cross the endothelium. The bearing of these studies on the pathogenesis of atherosclerosis will be discussed.

Lipoproteins and Atherosclerosis

John W. Gofman, Berkeley, Calif.

Division of Medical Physics, Donner Laboratory, University of California

Developments of the last few decades in physical chemistry of large molecules have provided a variety of technics and approaches to the characterization of biologically occurring macromolecules. The nature of serum lipids represents a subject readily amenable to study through the application of these developments. The ultracentrifuge has proven of particular value for this purpose, since by the choice of appropriate conditions of preparative and analytical ultracentrifugation the entire spectrum of lipid and lipoprotein components of serum can be studied quantitatively. Fractionation of the components is performed, utilizing the differences in density and migration rates which exist between them. The physicochemical and chemical properties of many of the isolated individual molecular species will be described in detail, together with the details of the methods for their isolation. The transport of cholesterol and its esters can be almost completely accounted for in the form of such high molecular weight components.

These lipid and lipoprotein molecules have been studied in presumably normal individuals and in those with atherosclerosis and certain other diseases associated with atherosclerosis. That certain of these molecules are in some way associated with atherosclerosis, at least of certain vascular beds, is definitely established. The detailed evidence for this will be given. These same lipoproteins are present with higher frequency and at greater concentration in hypertension, diabetes, nephrosis, and hypothyroidism than in normal subjects of corresponding age and sex categories, which is consistent with the clinical observations of incidence of atherosclerosis in such groups. The correlation of the concentration of the lipoproteins with the analytical serum cholesterol in the various disease categories and in normals will be presented.

As part of an over-all study of the nature and origin of these lipoproteins studies of the effect of diet and certain drugs on their blood level are in progress and will be described in detail. Possible endocrine aspects of the control of the metabolism of the various lipoproteins will be discussed.

The progress of research on the turnover rates of the various lipoproteins, as studied with tritium and P^{32} labels, will be reported

Ultracentrifuge and Electrophoretic Studies of Serum Lipoproteins in Relationship to Vascular Disease

Lena A. Lewis and Irvine H. Page, Cleveland, Ohio

Research Division of the Cleveland Clinic Foundation and Frank E. Bunts Educational Institute

The ultracentrifuge studies of Gofman and co-workers on lipid-lipoprotein concentrates of human sera, which showed the presence of a peak with the flotation rate S_f 3–7 in all sera, and an additional component in some sera with an S_f 10–20, have been confirmed. It has also been found, as he reported, that the concentration of the S_f 10–20 peak may be decreased by decreasing the amount of cholesterol in the diet to very low levels for a period of weeks.

The S_f 10–20 peak has been found in nearly all sera of patients with malignant hypertension and in patients following myocardial in-

farction. Electrophoretic analyses of the sera or plasma of these patients has shown (as was previously reported) a beta-globulin concentration above the normal level. The alpha-globulin was also markedly elevated following coronary occlusion. Modifications that occur immediately and over a long period of time following myocardial infarction in the lipid-lipoprotein pattern and the electrophoretic pattern will be reported.

The lipoproteins of dog sera, concentrated by ultracentrifugation, using high salt concentration as previously described (Lewis and Page), showed essentially the same pattern before adrenalectomy and after, when the dog was well maintained with adrenal extract. However, the lipoprotein concentration as judged by relative areas of the peaks, was much lower when the animals were in extreme adrenal insufficiency. The factors involved in producing the decreased lipoprotein concentration will be considered.

A study of the lipoprotein patterns of concentrates has shown a much higher concentration as judged by relative areas of peaks, in human and rabbit, than in dog and rat sera. The possible relationship of these differences to development of atherosclerosis in different species will be discussed.

The Comparative Metabolism of Dietary and Endogenous Cholesterol Differentiated By Use of Radioactive Carbon

R. Gordon Gould, Chicago, Ill.

Rush Department of Biochemistry, The Presbyterian Hospital

C^{14}-labeled cholesterol was prepared by biosynthesis, administered to rats and mice, and the fate of the C^{14} determined after varying periods of time. An appreciable fraction was demonstrated in the respiratory carbon dioxide and an unexpectedly large amount was found in the fecal fatty acid fraction (possibly as bile acids). Of the labeled cholesterol present in the body, a very small fraction was present in the blood, and about 15 per cent in the liver and the rest was distributed rather generally in the tissues.

The distribution and turnover rates of endogenous cholesterol were studied in a similar manner except that labeled acetate was administered. Synthesis of cholesterol occurs in many tissues, particularly intestinal mucosa, liver, and skin but not in aorta. As the specific activity of plasma free cholesterol rises relatively slowly, it is probable that transport of labeled cholesterol to certain tissues by the blood stream is not an important factor during the first few hours. After about four hours, the synthesis of labeled cholesterol has ceased and any changes in distribution after this time must be due to transport or to metabolic conversion. Results on more than ten tissues will be presented and compared with those from dietary cholesterol experiments.

Effect of Dietary Cholesterol on Rate of Cholesterol Synthesis in the Intact Animal Measured by Means of Radioactive Carbon

C. Bruce Taylor and R. Gordon Gould, Chicago, Ill.

Rush Department of Biochemistry, The Presbyterian Hospital

It was previously found that feeding of cholesterol in moderate amounts to dogs or rabbits for periods of 6–12 weeks decreased the rate of in vitro synthesis of cholesterol by liver slices but had little effect on in vitro synthesis by skin slices or intestinal mucosa.

Similar studies have been made on intact animals and it has been found that a single dose of cholesterol given several hours before the administration of labeled acetate results in a decreased rate of synthesis of cholesterol in all tissues examined in puppies (using littermate controls) and in rabbits. The effect was most marked in plasma, bile, liver, and adrenals and less so in intestine and skin.

Although both species respond to dietary cholesterol in the same manner, rabbits differ from dogs and also several other species in that they have normally a much slower rate of synthesis (and therefore of disposal) of cholesterol and this may be of significance in explaining their remarkable sensitivity to dietary cholesterol.

Rabbits with well-developed atheromatosis have been given labeled acetate and preliminary results indicate that the turnover of endogenous cholesterol is much faster in normal parts of the aorta than in atheromatous plaques.

The Effect of Salt-Induced Hypertension on Spontaneous Atherosclerosis in the Chick

Jeremiah Stamler and Louis N. Katz, with the technical assistance of Philip Johnson, Chicago, Ill.

Cardiovascular Department, Medical Research Institute, Michael Reese Hospital

Hypertension has been repeatedly implicated in the pathogenesis of arteriosclerosis. However, experimental data bearing upon this problem are meager. Recently this department demonstrated that salt feeding induces a significant blood pressure elevation in chicks. This finding made it possible for us to study the effect of chronic salt-induced hypertension on atherogenesis in this avian species.

Sixty 1 day old cockerels were used. One group had 0.9 per cent saline solution ad libitum substituted for drinking water; the second group received 3–8 per cent sodium chloride mixed with plain mash plus tap water ad libitum; the control group was given plain mash and tap water ad libitum.

Serial studies revealed a slowly developing, persistent blood pressure rise in about half the chicks receiving salt. The mean terminal blood pressure of these hypertensive chicks was 195/160 mm. Hg (controls: 160/135). Salt feeding also induced a chronic watery diarrhea, delayed growth and development and depressed comb size and color. The plasma cholesterol levels were normal.

At autopsy the incidence, extent and severity of spontaneous atherosclerosis were similar in the experimental and control birds. Hypertension therefore appeared to be ineffective in grossly accelerating or aggravating spontaneous atherogenesis in the chick.

Vascular Lesions in Alloxan Diabetic Rats

A. L. Chute, J. L. Orr, M. J. O'Brien and E. E. Jones, Toronto, Canada

Hospital for Sick Children

Rats made diabetic with alloxan and placed on high protein, high fat, or high carbohydrate diets failed to show any characteristic vascular changes up to 18 months following the onset of diabetes.

Rats made diabetic with alloxan and placed on normal diets with 10 per cent or 5 per cent added sodium chloride developed severe arterial lesions with nephrosclerosis, and hypertension in 4 to 6 months. The lesions resemble those described by Selye in unilaterally nephrectomized rats given a high sodium chloride

diet and exposed to stress. Depancreatized diabetic animals fed on a 10 per cent salt diet failed to develop these vascular lesions. Many survived only 1 to 2 months, though some lived 5 to 6 months.

Rats which had the renal arteries clamped during the period of alloxan administration developed diabetes but failed to show the vascular lesions when fed on the salt diet.

The lesions, therefore, appear to be due to the effect of a high salt diet in the presence of damaged kidneys. There is some evidence that control of the diabetes minimizes the vascular changes.

Experimental Arterial Lesions in Dogs Related to Diet and Renal Insufficiency

Russell L. Holman, New Orleans, La.

Department of Pathology, Louisiana State University School of Medicine

The sequence of feeding a "standard high fat diet" for eight weeks or longer, then inducing "standard renal insufficiency" in any of several ways, is regularly followed by "typical arterial lesions" in mongrel dogs regardless of age and sex. Either factor alone is ineffective. The pathogenesis of these arterial lesions, which closely resemble those of rheumatic arteritis and polyarteritis nodosa, is obscure but is being studied from the standpoints of a "dietary factor" and of a "renal factor." The dietary factor is: (1) found in certain animal fats (creamery butter, certain samples of cod liver oil, shark oil, and menhaden oil); (2) not present in olive oil, corn oil, coconut oil, lard, mutton tallow, and oleomargarine; (3) not vitamin A or vitamin D; (4) relatively heat stable; (5) destroyed or inactivated by saponification or by acetone separation; (6) unaffected by choline; and (7) inactivated or counteracted by vitamin E, by diamylhydroquinone, by cortisone, by cholesterol, or by omission of the high fat supplement for four weeks or longer. Additional data on the "dietary factor" will be presented.

The renal factor is related to an, as yet, undetermined metabolic activity of the proximal convoluted tubules.

In one dog, bilateral thyroidectomy and cholesterol feeding were superimposed on the above experimental procedures. A sustained hypercholesterolemia (roughly ten times the control level) developed and when this dog died in "uremia," instead of "typical arterial lesions," atheromata—sometimes combined with necrotizing arteritis—resulted.

Some of the implications of these experimental findings will be discussed.

The Granular Cells of the Renal Arteriole and Hypertension*

J. F. A. McManus, Charlottesville, Va.

Department of Pathology, University of Virginia School of Medicine

The granular cells of the renal arteriole have been suggested by Goormaghtigh as a source of renin. Recently Marshall and Wakerlin (Federation Proc. **8**: 106, 1949) have confirmed the coloration of these granules with the periodic acid-Schiff's method (McManus, 1947), and have pointed out that renin has similar coloring and solubility properties. The present report describes the search for the granular cells of the renal arteriole in a wide variety of kidney diseases.

Granular cells are prominent and numerous in acute (malignant) hypertension, the crush kidney and cirrhosis of the liver in series of

* Work done in the Department of Pathology, the Medical College of Alabama, Birmingham 5, Alabama.

cases. They have not been found in normal kidneys, in acute or chronic glomerulonephritis or pyelonephritis, in benign nephrosclerosis, in intercapillary glomerulosclerosis or in eclampsia. If the granular cells of the renal arterioles are the source of renin, various different mechanisms must be active in different types of hypertension. Some possibilities are discussed.

White Blood Cells in Old Age and in Arteriosclerosis

Rudolf Altschul, Saskatoon, Canada

Department of Anatomy, University of Saskatchewan

The number of lymphocytes decreases rapidly in infancy; later there is only a slight reduction, except for a transient presenile increase. It seems possible that metabolic changes which occur in old age and in arteriosclerosis are linked to variations in the white blood cell picture. This is being investigated. Preliminary studies show that patients with coronary occlusions have often a relative and absolute lymphopenia. In healthy old people the white blood cell count is rather low with a normal proportion of lymphocytes.

When rabbits are given pure cholesterol or a diet of milk and yolk, the number of neutrophils and lymphocytes increases. After cessation of the cholesterol administration, the white blood cell count does not return immediately to the norm. In this connection it should be mentioned that normal rats and mice have a higher percentage of lymphocytes than rabbits and guinea pigs (Kracke), although they belong to the same order (rodents). As is well known, rabbits and guinea pigs are susceptible to cholesterol arteriosclerosis, while rats and mice are not.

There are many dangers of technical errors and faulty interpretations of these findings, especially in the human material, and therefore no final conclusions are attempted at present.

Medial Degeneration of the Coronary Arteries of Chickens: Lesion or Artefact?

J. C. Paterson, London, Canada

Department of Medical Research of the University of Western Ontario

A number of photomicrographs will be shown in support of the contention that "hydropic degeneration" of the media of coronary arteries of chickens, considered to be the primary lesion of coronary sclerosis in this species, is a manifestation of disease and is not an artefact as suggested recently by Lindsay and Chaikoff (Arch. Path. **49**: 434, 1950).

Production of Experimental Cholesterol-Induced Atherosclerosis in the Chick with Minimal Hypercholesterolemia and Organ Lipidosis

Jermiah Stamler and Louis N. Katz, with the technical assistance of Christine Bolene, Chicago, Ill.

Cardiovascular Department, Medical Research Institute, Michael Reese Hospital

Since human atherosclerosis frequently occurs in people with presumably normal plasma and tissue lipid levels, we undertook to induce atherosclerosis in chicks with minimal hypercholesterolemia and organ lipidosis.

Fifteen cockerels maintained for 25–35 weeks on a mash enriched with $\frac{1}{4}$ per cent cholesterol plus 5 per cent cottonseed oil, were compared with controls fed plain mash. The cholesterol-enriched mash induced a minimal persistent

hypercholesterolemia (166 mg. per cent; controls: 99 mg. per cent); no significant alteration in plasma lipid phosphorus concentration; a rise in the ratio of plasma total cholesterol to lipid phosphorus; a moderate hepatic cholesterosis; and no consistent changes in lipid levels in the aorta and other organs.

Forty-two per cent of chicks fed ¼ per cent cholesterol-enriched mash for 35 weeks had gross atherosclerosis of the thoracic aorta (controls: 0 per cent); the incidence, extent and severity of atherosclerosis of the abdominal aorta was also greater in the experimental birds. Atherosclerosis in the thoracic aorta closely paralleled the level of hypercholesterolemia in individual chicks. No other correlations could be established between biochemical and pathological findings.

The presence of atherosclerosis in these birds with minimal dietary hypercholesterolemia and organ lipidosis lends further support to the concept of the relationship of cholesterol in general, and exogenous cholesterol in particular, to the pathogenesis of human atherosclerosis.

The Effect of Tween 80 on the Serum Lipids and the Tissues of Cholesterol-Fed Rabbits

Torrence P. B. Payne and G. Lyman Duff, Montreal, Canada

Department of Pathology, Pathological Institute, McGill University

As previously reported by Kellner and associates, the intravenous injection of Tween 80 into rabbits on a cholesterol-rich diet was found to produce an elevation of serum lipid phosphorus which was parallel to the rise of serum cholesterol, and the development of atherosclerosis was inhibited. However, in our experiments, the fatty acids of "neutral fat" were not markedly elevated. It is suggested that the high values for neutral fat reported by Ahrens and Kunkel are due to measurement of the injected circulating Tween 80 and that this substance therefore may of itself and independent of any serum lipid changes, have an inhibitory effect on the development of cholesterol atherosclerosis.

In the treated animals, the reticuloendothelial system, especially the spleen, showed an extremely marked engorgement with foam-cells which were also present in large numbers in the lumens of the blood vessels of the lungs and other organs. This abundance of foam-cells in the reticuloendothelial system and in the circulating blood with only a very slight development of atherosclerosis argues against the validity of the theory of Leary that the development of atherosclerosis depends on the entry of foam-cells from the blood stream into the arterial walls. In addition, there was marked swelling and fatty change in the cells of the proximal convoluted tubules, indicating that intravenous Tween 80 is not a bland substance.

Studies of the effect of the oral administration of Tween 80 supported our previous finding that the relationship of serum cholesterol to the other serum lipids is much more important than the absolute level of cholesterol itself.

The Effect of Choline and Inositol Upon Experimental Canine Arteriosclerosis

Jack D. Davidson, Walter Meyer and Forrest E. Kendall, New York, N. Y.

Columbia Research Service, Goldwater Memorial Hospital

Studies have been made of the effect of choline and inositol upon the arteriosclerosis produced in dogs by an experimental regimen of cholesterol and thiouracil feeding. Among

animals carried on the regimen for 14 months, those which received 5 Gm. choline hydrochloride daily had as much arteriosclerosis as controls, which received no added choline. In a group of dogs on the experimental regimen for 4 months, those which received 2½ per cent choline hydrocholoride in their diet did not differ from the control animals with respect to serum lipid levels, resultant arteriosclerosis or degree of lipid infiltration of the livers. Reports will also be made on the effects of inositol in similar experiments, and on the influence of choline upon the regression of arteriosclerotic lesions following discontinuance of the cholesterol-thiouracil feeding.

The Relationship between the Phospholipids and the Cholesterols in Human Plasma

Raymond S. Jackson, Charles F. Wilkinson, Jr., Eugene A. Hand, A. M. Waldron and William C. Vogel, New York, N. Y.

Department of Medicine, New York University Post-Graduate Medical School

The relationship between the phospholipids and the cholesterols in plasma has been examined on the basis of 242 determinations in a group of normal human subjects, and in a variety of disease states. A most consistent relationship has been found to exist between the phospholipids and free cholesterol, which appears to be independent of the disease process. No such relationship could be demonstrated between phospholipids and total or esterified cholesterol.

With elevation of the free cholesterol, there is a decrease in the proportionate amount of phospholipid. The rate of decrease, rapid at first, approaches zero when the PL/FC ratio has declined to the point where equimolar quantities of phospholipid and free cholesterol exist. Further increases of free cholesterol do not disturb this equimolar relationship. It is postulated that though cholesterol may be released into the plasma in quantities exceeding this equimolar ratio, the excess is treated as an abnormal substance and sequestered from the blood stream. An attempt is made to relate these findings to the subject of atheromatosis.

The Phospholipid/Cholesterol Ratio as a Test for Atherosclerosis

Lester M. Morrison, P. Gonzalez and E. Wolfson, Los Angeles, Calif.

Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists

Kellner, Correll and Ladd, and Ahrens and Kunkel have found that the phospholipid/cholesterol ratio of the serum is directly related to the development of atherosclerosis. The latter authors have found that in normal subjects the ratio of serum lipid phosphorus (expressed as lecithin) to the serum cholesterol is 1 or more than 1. In developing atherosclerosis this ratio is believed to fall to less than 1.

The authors studied the phospholipid/cholesterol ratio in over 300 subjects, comprising normal individuals, patients with miscellaneous diseases and patients with recent, proved coronary thrombosis and myocardial infarction (i.e. with proved coronary atherosclerosis). It was found that the majority of normal individuals have a phospholipid/cholesterol ratio substantially higher than patients with active coronary atherosclerosis. It was further noted that the majority of patients with active coronary atherosclerosis have a phospholipid/cholesterol ratio of less than 1.

The recent findings are reviewed of White, Edwards and Dry, and Morrison and Gonzalez that the majority of individuals in the fourth to sixth decades of life and after already have or are developing active coronary atherosclerosis; the relationship to phospholipid/cholesterol ratio is discussed and its limitations and values considered.

Atherosclerosis of Early Age: Clinical and Pathological Studies

David Adlersberg and F. G. Zak, New York, N. Y.

The Medical Services and The Laboratories, Division of Pathology, of the Mt. Sinai Hospital

A group of fifty persons below the age of forty-six who died of coronary artery occlusion came to autopsy in the past twenty-two years at Mount Sinai Hospital. This group was compared with a group of fifty individuals sixty years and over with the same cause of death.

The younger group was characterized by the following clinical features: A striking familial occurrence of heart disease; a shorter clinical history and average duration of anginal pain and cardiac failure; a greater preponderance of males, and a greater incidence of obesity among the females; a high incidence of heavy smokers among the men; a significantly lower incidence of hypertension and diabetes (one fourth to one third of that found in the older group); higher levels of serum cholesteral (348 mg. per 100 ml. versus 275).

The pathological features of the younger group were as follows: A greater occurrence of extremely heavy hearts (500 Gm. and more) despite the high incidence of hypertension in the older group; this finding could be related to the reduced body weight especially among old females; while among the old a certain parallelism was present between the severity of coronary and systemic arteriosclerosis such behavior was seen infrequently in the young.

The microscopic differences of the coronary arteries were less impressive, making it impossible to separate morphologically the two age groups. However, the youngest patient of the young (a 27 year old male) revealed the presence of a stenosing coronary process with an acute arteritis.

To supplement this striking observation a group of young persons who died suddenly and were autopsied by the Chief Medical Examiner of New York City were studied through the kind cooperation of Dr. Milton Helpern. Among these a considerable number showed similar inflammatory lesions in the coronary arteries, identical with those described as stenosing coronary arteritis by von Albertini in Switzerland. Microphotographs of the lesions will be presented and the clinical implications of these findings discussed.

The Age Factor in Cholesterolemia and Atheromatosis in the Chick

Simon Rodbard, Christine Bolene, Ruth Pick, Martin Lowenthal, Gerard Gros and Louis N. Katz, Chicago, Ill.

Cardiovascular Department, Medical Research Institute, Michael Reese Hospital

We have recently investigated the relative roles of maturation and aging in the regulation of plasma cholesterol and in the tendency to atheromatosis in newly hatched chicks. On a standard mash diet the cholesterolemia falls below 100 mg. per cent in one week and is maintained at this level. Occasional chicks show transient minimal atheromatosis in the first week.

When day-old chicks are given a mash diet supplemented with 2 per cent cholesterol and 5 per cent oil, cholesterolemia is maintained at 300–500 mg. per cent for the first 7 weeks. Estrogens produce an endogenous hypercholes-

terolemia of like degree. At the eighth week, the plasma cholesterol level rises markedly despite no change in the feeding regime. Microscopic atheroma of the smaller coronary vessels are observed as early as 5 weeks of life. At 15 weeks, marked gross coronary atheromatosis has evolved through stages of fibrosis, calification and bone formation.

These experiments show that atherosclerosis can be induced in very young chicks, before factors associated with aging have had time to operate. Doubt is therefore cast upon the concept that injury to the arterial wall must precede cholesterol deposition and atherogenesis. Identical diets are seen to produce markedly varying degrees of cholesterolemia at different ages. The role of endogenous mechanisms affecting cholesterolemia and atherogenesis is thus emphasized.

Factors in the Development of Premature Vascular Disease in Young Diabetics

Howard F. Root and James L. Wilson, Boston, Mass.

A study of patients whose diabetes began between infancy and the age of 25 years with respect to vascular disease is based on the cooperative efforts of the internists, the ophthalmologists, roentgenologists and the chemical laboratory. This series of 500 patients has been studied with particular reference to the duration of diabetes and the type of its control. The development of retinal lesions, nephrosclerosis of the Kimmelstiel-Wilson type and calcified vessels have been particularly observed. Photography of retinal lesions has been carried out. The patients were classified with respect to the type of control on the basis of: (1) the use of insulin within one year of onset or, by contrast, delayed use of insulin; (2) the cooperation of the patient in carrying out prescribed diet and insulin treatment; (3) frequency of medical observation and laboratory tests of blood and urine; (4) presence or absence of diabetic acidosis; (5) character of blood and urine tests.

Determinations of the lipids of the blood, especially lipid phosphorus, have been made particularly in a group where after 12 years of diabetes vascular and renal changes were beginning. The results indicate a relation between the degree of diabetic control and those factors which lead to premature changes in the arteries, small veins of the retina and the capillaries.

Serum Lipids and Atherosclerosis in Diabetes Mellitus

Julius Pomeranze and Henry G. Kunkel, New York, N. Y.

New York Medical College and the Hospital of the Rockefeller Institute for Medical Research

Two groups of unselected diabetic patients were studied. In group one, the sera of 50 patients were studied for complete lipid fractions. In group two, total lipids were done in a series of 223 patients. In a few patients with high serum lipids electrophoretic patterns were compared with normal patterns.

In both groups, elevation of serum lipid was found in approximately 50 per cent of patients studied. In both groups, when severe atherosclerosis was present, hyperlipemia was associated with it in more than 72 per cent of cases. The recent emphasis on phospholipid/cholesterol ratio in the genesis of atherosclerosis led to a study of this factor. In group one, 92 per cent of all patients with atherosclerosis showed the presence of some serum lipid abnormality. When marked hyperlipemia occurred, the greatest elevation was in the neutral fat fraction. Cholesterol levels in many cases gave no indication of total lipid elevation. No relationship could be found between control of diabetes, age of patient, duration of diseases, liver enlargement or sex and serum lipid levels.

Incidence of Hereditary Hypercholesterolemia

David Adlersberg, Louis E. Schaefer, Stanley R. Drachman, and Rhoda Dritch, New York, N. Y.

The Mount Sinai Hospital

A hereditary disturbance of lipid metabolism may be considered to be a predisposing factor in the genesis of certain forms of atherosclerosis. Studies in families with xanthomatosis as well as in young individuals with coronary artery disease support this concept.

It was of interest therefore to attempt to estimate the incidence of disturbed lipid metabolism, as manifested by hypercholesterolemia, in the general population. Accordingly, consecutive unselected admissions to male and female medical wards were surveyed. On admission a careful personal and family history was obtained, and a physical examination was done, with particular attention to the signs and symptoms of diseases due to a disturbed lipid metabolism. The following morning a fasting blood specimen was drawn, and serum cholesterol was determined by the Sperry-Schoenheimer method, the normal range of which is considered to be 160–240 mg. per 100 ml. We considered values of over 280 mg. to be hypercholesterolemic.

Whenever the history, the physical examination, or the serum cholesterol level of the patient suggested that familial hypercholesterolemia might be present, all available family members were surveyed in a similar way.

This report presents the results obtained to date in 200 index patients, 100 males and 100 females. The age of the men ranged from 18 to 79 years, average 48.4 years. The women ranged in age from 12 to 80 years, with an average of 46.5 years. The basic diseases of the patients were as follows: cardiovascular-renal—40 men, 38 women; infectious—18 men, 15 women; neoplastic—10 men, 6 women; endocrine—3 men, 11 women; other diseases—29 men, 30 women.

The cholesterol level of the male group ranged from 111 to 512 mg. per cent with an average of 224.5 mg. per cent. Twenty-one of the men had a serum cholesterol in excess of 280 mg. per cent. Among the females the range was from 109 to 655 mg. per cent, with an average of 240.9 mg. per cent. Of these, 27 were over 280 mg. per cent.

In the group of 100 males there were six instances in which two or more family members had hypercholesterolemia. In addition, there are three families still under investigation in which the index patient had hypercholesterolemia.

Among the females there were four families in which at least two members had cholesterol levels in excess of 280 mg. per cent, and there are five additional families under investigation.

Thus, a preliminary survey of the population of a large general hospital has disclosed an incidence of hereditary hypercholesterolemia of 5 per cent. This figure will probably be higher with the completion of studies of the families still being investigated.

The Effects of Low Fat-Low Cholesterol Diets on the Serum Lipids

Lester M. Morrison, M. Zwierlein and E. Wolfson, Los Angeles, Calif.

Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists

Various observers have recently offered evidence that ingested fat and cholesterol in the diet contribute significantly to the development of human atherosclerosis. It has also been

shown that lipid metabolism has a dual character, involving both exogenous and endogenous cholesterols and fats. Since cholesterol and fat are known to be implicated in the development of atherosclerosis, a study was undertaken to determine what the effect of a low fat–low cholesterol diet would be on serum lipids and lipoproteins in a series of (1) normal individuals, (2) patients with miscellaneous diseases and (3) patients with coronary atherosclerosis, over periods of time extending up to four years.

Determinations were made especially on total serum lipids, total cholesterol, cholesterol esters, cholesterol esterases, phospholipids, neutral fats, and chylo- and lipomicron counts.

It was noted that it is possible with this diet to reduce the various components of the serum lipid and lipoprotein fractions in many normal individuals, patients with miscellaneous diseases and with coronary atherosclerosis when the diet is carefully adhered to, particularly over periods extending from one to four years. Series of normal subjects and patients were encountered, however, in which this did not occur for reasons discussed, related to the essential familial hypercholesterolemia of Wilkinson, disorders in liver functions involving lipid and lipoprotein metabolism, and the intestinal absorption of fats and cholesterol.

Studies in Clinical Atheromatosis. IV. Important Roentgenologic Signs

Joseph B. Wolffe, Philadelphia, Pa.

Wolffe Clinic and Hospital

One hundred patients showing one or more signs of the atheromatous syndrome were studied roentgenologically. Teleradiographic studies of the thoracic aorta were correlated with lateral bucky films of the abdominal aorta.

This study revealed that the abdominal aorta is the site of predilection for the earliest appearance of atheromatous changes. The procedure is simple, inexpensive and adds greatly to the chain of evidence for the clinical recognition of the atheromatous syndrome.

A Comparison of Aging Processes in the Pulmonary Artery and Aorta

H. T. Blumenthal, Fred P. Handler, Jack Zuckner and S. H. Gray, St. Louis, Mo.

Department of Pathology, St. Louis University, School of Medicine, The Laboratory of the Jewish Hospital, and the Snodgras Laboratory, City Hospital

A comparison by decades of aging processes in the thoracic and abdominal portions of the aorta with those in the main pulmonary artery has been carried out. A basic anatomical difference between the character and arrangement of elastic fibers in these two vessels has been noted, as well as differences in their age-changes. The latter are related to differences in the intensity and rate of calcification of the media. The abdominal aorta shows the most severe changes and the pulmonary the least marked; the thoracic portion of the aorta shows a progression of intermediate severity. Chemical data consisting of the percentages of total ash and calcium ash are correlated with the morphological observations.

Spontaneous Canine Arteriosclerosis

Margaret Bevans, Bruce Taylor* and Liese L. Abell, New York, N. Y.

*Columbia Research Service, Goldwater Memorial Hospital, (*and Department of Pathology, Rush Memorial School, Chicago, Ill.)*

Spontaneous intimal arteriosclerosis in elderly dogs occurs more frequently than is noted in the meager literature on the subject. Studies of dogs of known age indicate that certain anatomical changes take place in the intima of the arteries which are analogous to those seen in the arteries of aging human beings. The relationship of these alterations to the formation of spontaneous arteriosclerotic plaques and to the experimental lesions of dogs on a thiouracil-cholesterol regimen will be discussed.

Plasma Iodine Fractions and Plasma and Hepatic Cholesterol in Rabbits

Helen Bennett Brown and Irvine H. Page, Cleveland, Ohio

Research Division and Frank E. Bunts Education Institute, Cleveland Clinic Foundation

Administration of iodine as potassium iodide aids in preventing deposition of cholesterol in experimental atherosclerosis in rabbits. Thyroxine is also known to decrease plasma cholesterol and, like iodide, to protect against cholesterol atherosclerosis. Furthermore, iodine can react with proteins to form products which have the activity of thyroxine. The effect of iodide feeding might thus be attributable to thyroidal and extrathyroidal formation of thyroxine-like material. The purpose of this study was to examine this possibility by fractional analyses of plasma iodine and correlation of these with plasma total and hepatic ester cholesterol.

The iodine content of the various plasma fractions was analysed by the method of Barker and the fractionation of the protein-bound iodine followed essentially the technic described by Taurog and Chaikoff. It was found that plasma inorganic iodine, as well as protein-bound iodine, increased progressively with increasing dosage. The alkali-washed butanol soluble fraction of the protein-bound iodine, of which thyroxine is one component, remained normal at daily dosages of 1, 20 and 40 mg. iodine in both normal and thyroidectomized rabbits. A portion of the protein-bound iodine which is *insoluble* in butanol appeared in the plasma of thyroidectomized controls and in normal rabbits receiving iodide. In both normal and thyroidectomized animals this insoluble fraction increased with iodide dosage.

One of the effects of iodide upon the cholesterol metabolism is maintenance of relatively normal concentrations of plasma total and hepatic ester cholesterol. This effect is independent of the thyroid gland and thyroxine-like material of plasma occurring in alkali-washed butanol soluble fraction of protein-bound iodine. Rather, the effect of iodide treatment on cholesterol metabolism is associated with an increase in other fractions of the plasma iodine, namely, the inorganic and butanol-insoluble fractions. These data emphasize the lack of correlation between total plasma protein-bound iodine, thyroid activity and abnormal iodine intake.

Further Studies on the Human Aortic Phosphatase

John Esben Kirk and Elith Praetorius, St. Louis, Mo.

Division of Gerontology, Washington University School of Medicine

In a previous investigation (Science **111**: 334, 1950) the presence in the media of the human aortic wall of a phosphatase, capable of splitting disodium phenylphosphate and having an

optimum activity at pH 5.7–5.8 was reported.

Further studies on this enzyme have revealed that the phosphatase is also capable of splitting disodium p-nitrophenylphosphate, and that sodium fluoride in 8 mM concentration per liter produces a considerable inhibition. No measurable inhibition was exerted by cupric sulfate (1 mM per liter), monoiodoacetic acid (3 mM per liter), dipyridyl (3 mM per liter) or cyanide (3 mM per liter).

In order to investigate the possible effect of dialysis on the phosphatase activity samples of the supernatant preparations were placed in cellophane bags and dialyzed for 24 hours at 1–2 C. during constant stirring against successive portions of glass distilled water. A comparison of undialyzed and dialyzed samples from the same aorta showed no difference in cleavage of the substrate. A low oxygen tension produced by evacuation of the samples contained in Thunberg tubes or by passing through a current of inert gas was also without influence on the phosphatase activity.

Since determination of the hemoglobin content of the cream-colored tissues homogenates by the method of Van Slyke and Neill failed to reveal measurable amounts of hemoglobin in the samples it seems improbable that the phosphatase activity of the aortic media is derived from the presence of erythrocytes in the aortic tissue.

No essential difference was found between the phosphatase activity of suspensions obtained from young and from old individuals, nor between samples obtained a few hours after death and samples stored for 24 to 48 hours. Suspensions derived from different layers of the media of the same aorta also showed practically the same enzyme activity.

A Clinical Comparison of Three Tests for Atherosclerosis

Lester M. Morrison, Harry Sobel and E. Wolfson, Los Angeles, Calif.

Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists

A comparative study was made in over 500 subjects of three laboratory tests which have been proposed as methods for the detection of active atherosclerosis in human subjects. These three tests are (1) the phospholipid/cholesterol ratio of the blood serum as proposed by Ahrens and Kunkel of the Rockefeller Institute. In normal human subjects the ratio of serum lipid phosphorus (expressed as lecithin) to the total serum cholesterol has been found to be one or more than one, usually. In human subjects with active atherosclerosis this ratio has usually been found to fall below one. (2) The optical ultracentrifuge method of Gofman and co-workers at the University of California. This procedure entails the centrifuging of blood serum at over 52,000 revolutions per minute and detecting the presence of giant lipid and lipoprotein molecules of low density pathognomonic of active atherosclerosis. (This aspect was presented through the cooperation of Dr. Gofman and co-workers.) (3) A cholesterol partitioning method proposed by Sobel and Morrison depends on the liberation of cholesterol by saponin from the bound protein in the lipoprotein molecular complex. The cholesterol exists in a firmly bound protein state and loosely bound or free unstable colloidal states. It was found that in the normal subject the cholesterol is firmly bound to the protein molecular complex in from 60–100 per cent of the total cholesterol and that in patients with developing atherosclerosis this percentage fell to from 0 to 50 per cent. The authors found that there was no correlation between the total amount of cholesterol in the blood and the state of the cholesterol in the lipoprotein complex.

These three tests were found to be clinically useful in the detection of atherosclerosis and valuable in serving as a guide to therapy and prognosis. Their limitations and clinical application are discussed.

The Effect of Lipotropic Agents (Choline, Inositol) and Estrogenic Hormones in Serum Lipid Fractions

Lester M. Morrison and E. Wolfson, Los Angeles, Calif.

Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists

Lipotropic agents such as choline and inositol have been reported by various observers to prevent both experimental and human atherosclerosis. Similar findings have been reported with estrogenic hormones.

The mechanism of this action was studied in a series of over 100 human subjects, by analysis of serum lipid fractions before and after treatment with choline, inositol and estrogenic hormones over various periods of time. These subjects were normal individuals, patients with miscellaneous diseases and patients with coronary atherosclerosis. It was found that these latter agents increase the serum phospholipid ratio to serum cholesterol.

The total serum lipids and serum cholesterol of all cases studied showed variable types of behavior. Although many individuals displayed a tendency towards significant reductions in these latter serum levels, one group showed little or no change in these and another group actually displayed an increase in all lipid fractions under therapy.

It was concluded that one significant reason for the therapeutic results secured on the above lipotropic therapy was the relative increase in serum phospholipid level and turnover, which effected a stabilizing, dispersing action on serum cholesterol and neutral fats.

The Relationship of Cholesterol Esterase to Atherosclerosis

Lester M. Morrison, E. Wolfson and P. Berlin, Los Angeles, Calif.

Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists

Because of recent investigations demonstrating the significant role of lipids and lipoproteins in the development of atherosclerosis, a study was made of the behavior of a lipid enzyme in atherosclerosis. Cholesterol esterase determinations were made according to the method of Sperry in a series of 100 normal subjects, 100 patients with miscellaneous diseases and 100 patients with recent proved coronary atherosclerosis. Sperry discovered that in normal subjects when free cholesterol is incubated for from 24 to 72 hours, a fraction undergoes conversion to cholesterol esters. This conversion is effected by the action of cholesterol esterase.

The authors found that in normal subjects cholesterol esterase activity differs from that in atherosclerotic patients. Most normal persons have approximately 30 per cent of free cholesterol converted into cholesterol esters following 72 hours incubation of cholesterol at 37 C. Most patients with active coronary atherosclerosis fail to make the normal conversion. The recent report of Turner et al. indicates that this esterase function is determined and regulated by the liver. The practical possibilities of cholesterol esterase determinations in clinical practise are discussed.

The Effect of Ingested Aluminum Hydroxide on Cholesteremia and Atheromatosis in the Chick

Simon Rodbard, Christine Bolene, Ruth Pick and Louis N. Katz, Chicago, Ill.

Cardiovascular Department, Medical Research Institute, Michael Reese Hospital

We have attempted to influence the intestinal absorption of cholesterol by the addition of a specially prepared nonreactive aluminum hydroxide gel to the diet. In control chicks,

receiving the gel, no significant effect on the plasma cholesterol level was noted. Chicks fed a mash supplemented with 2 per cent cholesterol plus 5 per cent oil (C-O) developed hypercholesterolemia and atheromatosis. Animals receiving a similar C-O diet to which 1 to 8 per cent aluminum hydroxide gel was added showed consistent reductions in the plasma cholesterol level. The rate of development of the lesions was retarded in the treated animals.

Addition of the gel to a normal mash diet resulted in a significant decrease in the hypercholesterolemia resulting from injections of estradiol. The onset of the lesions was also delayed.

Aluminum hydroxide gel is therefore effective in reducing cholesterolemia and in delaying the onset of atheromatosis.

The Action of Saponin upon Serum from Atherosclerotic and Nonatherosclerotic Individuals

Harry Sobel and Lester M. Morrison, Los Angeles, Calif.

Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists

Tayeau reported that saponin liberates serum cholesterol from its combination with protein and that the cholesterol becomes quantitatively extractable with ether. This principle was applied in an effort to learn if the cholesterol-lipoprotein complex of serum could be studied thereby. When increasing quantities of saponin are added to serum and the mixture is shaken with chloroform, the fraction of the total cholesterol which may be extracted by chloroform increases until extraction is complete. When 0.2 cc. of a 9.00 per cent saponin solution is added to 0.2 cc. of serum and the mixture is shaken for 30 minutes with chloroform, it is found that there is an increased frequency of low extraction fractions in individuals with coronary heart disease. Thus 23 per cent of normal individuals and 37 per cent of individuals with miscellaneous conditions had extraction fractions below 60 per cent, while 75 per cent of individuals with coronary disease were in this category. When the mixture is allowed to stand for 30 minutes after shaking, it is found that the per cent of the aqueous phase which is occupied by emulsion is high when the sera of individuals with coronary disease has been used. The cholesterol extraction fraction is inversely related to the degree of emulsification. The emulsification may be due to the presence of an easily denatured protein.

The Effect of Desoxycorticosterone on Cholesterol Metabolism and Atherosclerosis in the Chick

Jeremiah Stamler and Louis N. Katz, with the technical assistance of Eva Levinson, Marilyn Dudley and Grady Crowley, Chicago, Ill.

Cardiovascular Department, Medical Research Institute, Michael Reese Hospital

Since adrenal steroids and particularly desoxycorticosterone (DCA) have been implicated in the pathogenesis of arteriosclerosis, we undertook to study the effect of DCA on avian cholesterol metabolism and atherogenesis. Twenty-four cockerels were given daily subcutaneous injections of DCA for the first 15 weeks of life. At 5 weeks, the diet of half of these was enriched with 2 per cent cholesterol plus 5 per cent cottonseed oil.

The four groups of chicks, DCA treated and controls, had similar patterns of feed intake and weight change. The 2 DCA treated groups exhibited persistent polydipsia and polyuria, and inconstant elevations in blood pressure. The cholesterolemias corresponded closely in the paired groups.

At autopsy the DCA chicks exhibited hypoplasia of the adrenals, testicles and combs; and myocardial hypertrophy. They had only slightly more severe cholesterol-induced and spontaneous atherosclerosis than the controls.

Apparently chronic administration of desoxycorticosterone is without marked effect on cholesterolemia and atherogenesis in the chick.